L5 ANSWER 1 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2006:1124678 CAPLUS Full-text
DN 145:455035
TI Preparation of pyrrolobenzodiazepine derivatives for treatment of proliferative diseases
IN Gregson, Stephen John; Howard, Philip Wilson; Chen, Zhizhi
PA Spirogen Limited, UK
SO PCT Int. Appl., 77pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2006111759	A1	20061026	WO 2006-GB1456	20060421
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	AU 2006238686	A1	20061026	AU 2006-238686	20060421
	CA 2604805	A1	20061026	CA 2006-2604805	20060421
	GB 2439881	A	20080109	GB 2007-20721	20060421
	EP 1879901	A1	20080123	EP 2006-726846	20060421
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	IN 2007DN07862	A	20071109	IN 2007-DN7862	20071011
	KR 2008004618	A	20080109	KR 2007-727047	20071120
PRAI	GB 2005-8084	A	20050421		
	GB 2005-22746	A	20051107		
	WO 2006-GB1456	W	20060421		

OS MARPAT 145:455035
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. with general formula I [wherein: R2 = (un)substituted aryl; R6 and R9 = independently H, R, OH, OR, SH, SR, NH2, NHR, NRR', nitro, Me3Sn, or halo, where R and R' = independently (un)substituted alkyl, heterocyclyl, or aryl; R7 = H, R, OH, OR, SH, SR, NH2, NHR, NHRR', nitro, Me3Sn, or halo; Z = alkylene; X = O, S, or NH; n = 2 or 3] or pharmaceutically acceptable salts or solvates thereof are prepared for the treatment of proliferative diseases. For example, compound II•2Na was prepared in a multi-step synthesis. II•2Na showed IC50 of 1.5 nM in the In Vitro cytotoxicity test with K562 human chronic myeloid leukemia cells.

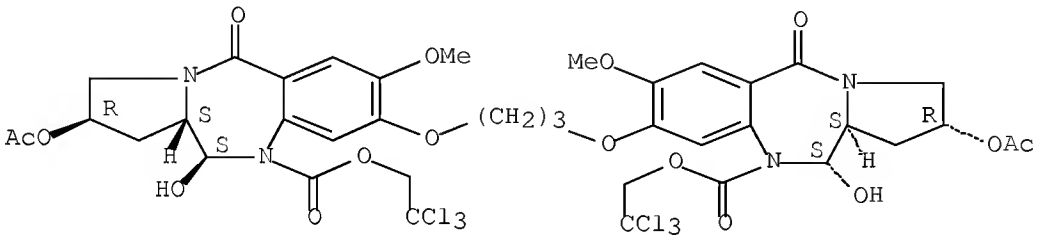
IT 864755-08-8P 864755-09-9P 864755-10-2P
864755-11-3P 913262-34-7P 913262-35-8P
913262-36-9P 913262-37-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of pyrrolobenzodiazepine derivs. for treatment of proliferative
diseases)

RN 864755-08-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

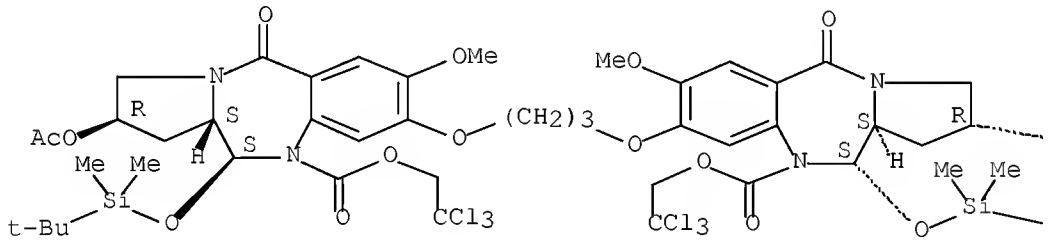


RN 864755-09-9 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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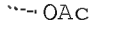
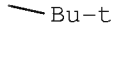
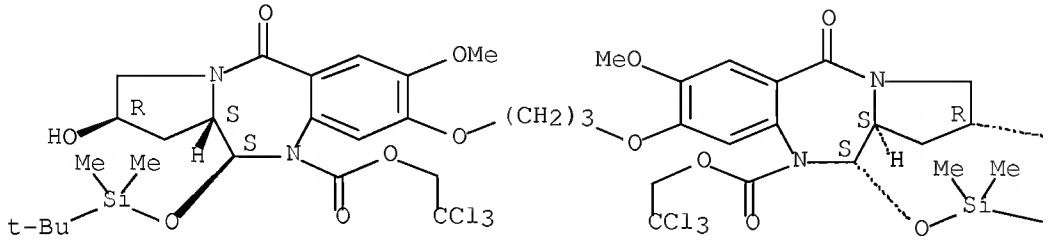




RN 864755-10-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-2-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

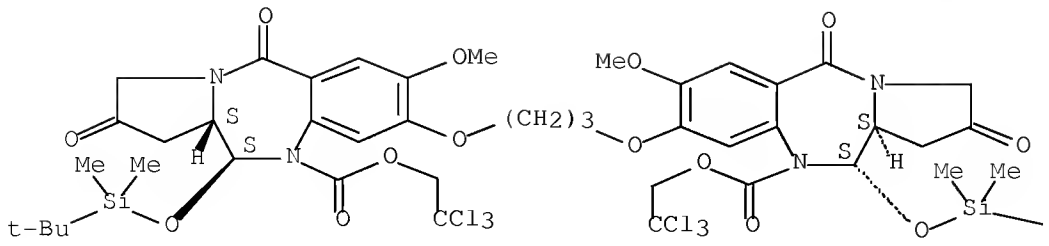
····OH

—Bu-t

RN 864755-11-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-2,5-dioxo-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

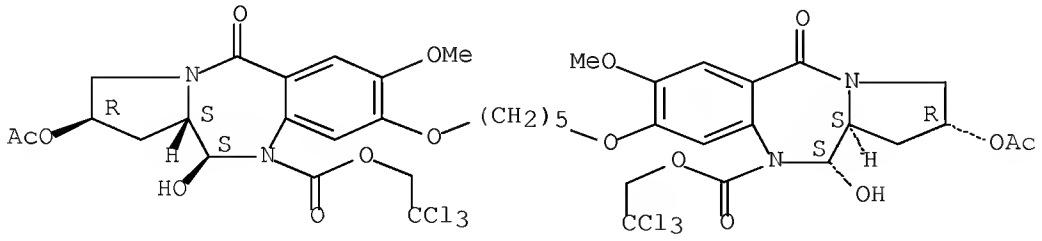


PAGE 1-B

—Bu-t

RN 913262-34-7 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2-(acetyloxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

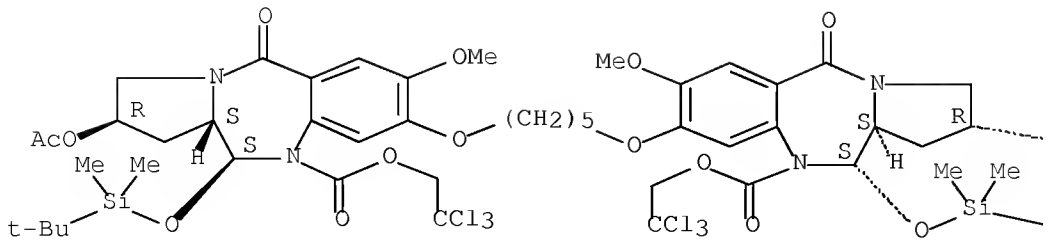
Absolute stereochemistry.



RN 913262-35-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2-(acetyloxy)-11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

OAc

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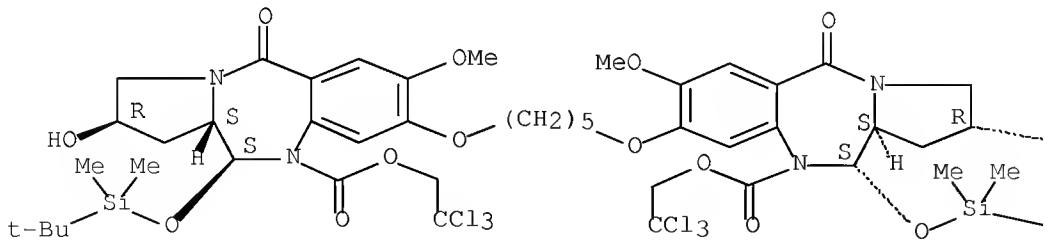
RN 913262-36-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-2-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

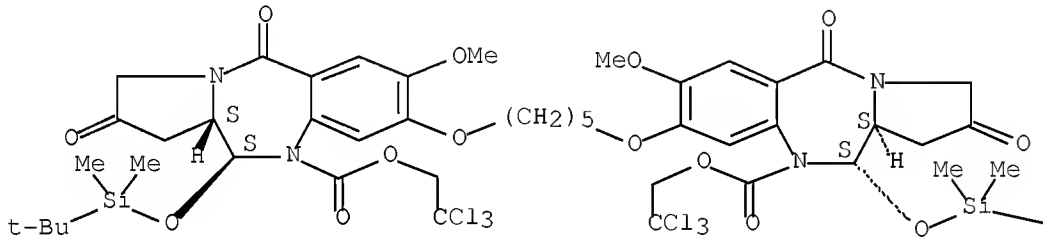
OH

Bu-t

RN 913262-37-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-2-hydroxy-7-methoxy-2,5-dioxo-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

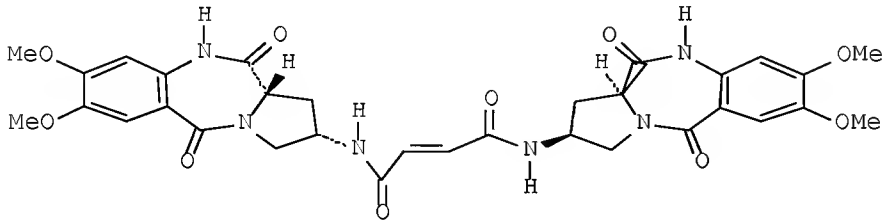


PAGE 1-B

Bu-t

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2006:854897 CAPLUS Full-text
DN 145:419101
TI Facile synthesis of pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione dimer
AU Al-Said, Naim H.
CS Department of Applied Chemical Sciences, Jordan University of Science and Technology, Irbid, 22110, Jordan
SO Journal of Heterocyclic Chemistry (2006), 43(4), 1091-1093
CODEN: JHTCAD; ISSN: 0022-152X
PB HeteroCorporation
DT Journal
LA English
OS CASREACT 145:419101
GI



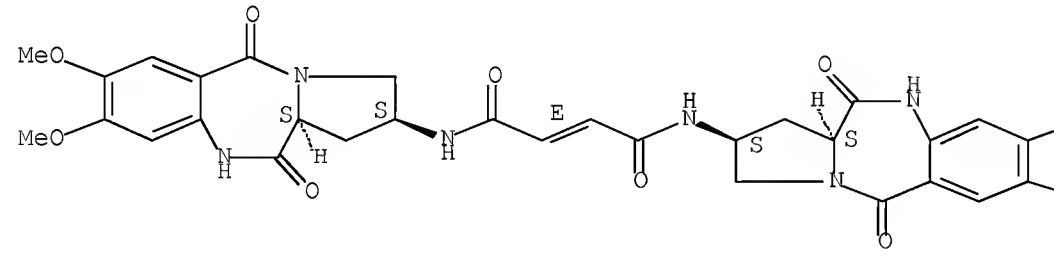
I

AB Efficient synthesis of a biol. important pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione dimer (I) linked through the C-2 positions by fumarate group is described.

IT 912289-35-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione dimer)
RN 912289-35-1 CAPLUS
CN 2-Butenediamide, N,N'-bis[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7,8-dimethoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-, (2E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

PAGE 1-A



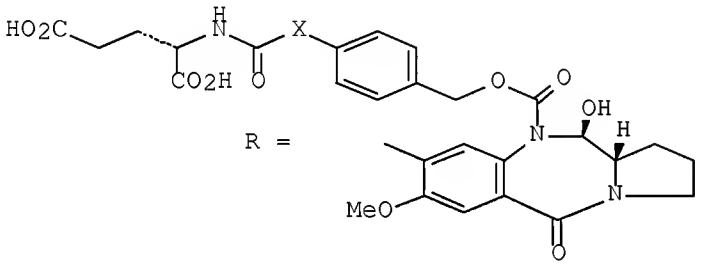
PAGE 1-B

OMe

OMe

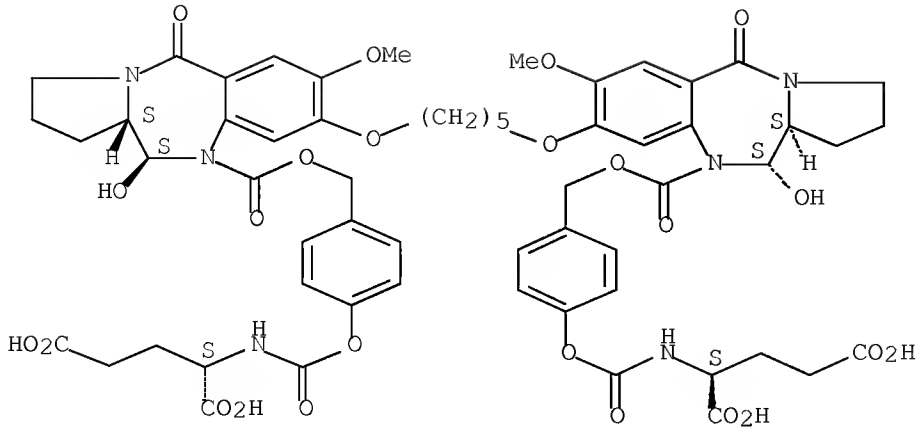
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1251578 CAPLUS Full-text
DN 144:150340
TI Synthesis and biological evaluation of novel pyrrolo[2,1-c][1,4]benzodiazepine prodrugs for use in antibody-directed enzyme prodrug therapy
AU Masterson, Luke A.; Spanswick, Victoria J.; Hartley, John A.; Begent, Richard H.; Howard, Philip W.; Thurston, David E.
CS CR-UK Gene Targeting Drug Design Research Group, School of Pharmacy, University of London, London, WC1 1AX, UK
SO Bioorganic & Medicinal Chemistry Letters (2006), 16(2), 252-256
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier B.V.
DT Journal
LA English
OS CASREACT 144:150340
GI



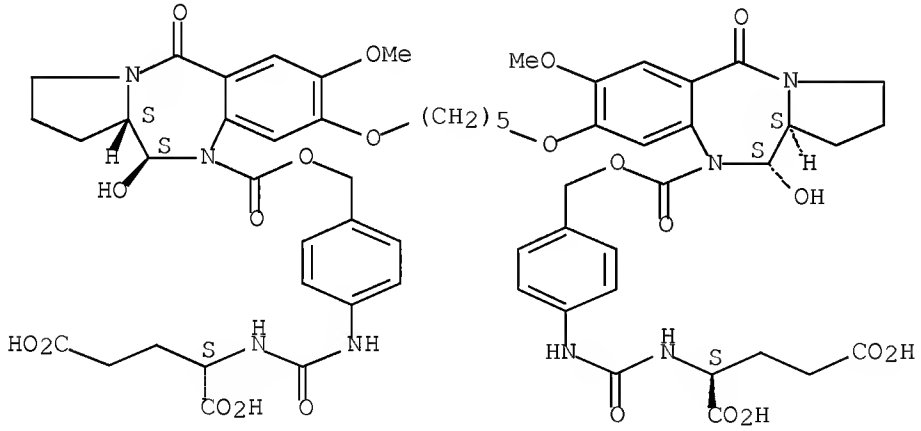
AB The design, synthesis and evaluation of four novel pyrrolo[2,1-c][1,4]benzodiazepine (PBD) prodrugs ROMe and RO(CH2)3OR [X = O, NH] for potential use in carboxypeptidase G2 (CPG2)-based antibody-directed enzyme prodrug therapy (ADEPT) is reported. Although all four prodrugs were shown to be less cytotoxic than the released parent PBDs, the urea prodrugs were found to be too unstable for use in ADEPT, whereas the carbamates are both stable in an aqueous environment and are good substrates for CPG2.
IT 848004-84-2P 848004-85-3P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and biol. evaluation of pyrrolo[2,1-c][1,4]benzodiazepine prodrugs for use in antibody-directed enzyme prodrug therapy)
RN 848004-84-2 CAPLUS
CN L-Glutamic acid, N,N'-[1,5-pentanediylbis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneoxycarbonyl]]bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 848004-85-3 CAPLUS
CN L-Glutamic acid, N,N'-[1,5-pentanediylbis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1004755 CAPLUS Full-text
DN 143:306350
TI Preparation, DNA crosslinking reactivity, antitumor and antibacterial activity of pyrrolobenzodiazepine dimers
IN Howard, Philip Wilson; Gregson, Stephen John; Taylor, Peter William; Thurston, David Edwin; Hadjivassileva, Tsveta Stepanova
PA Spirogen Limited, UK
SO PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005085260	A1	20050915	WO 2005-GB915	20050309
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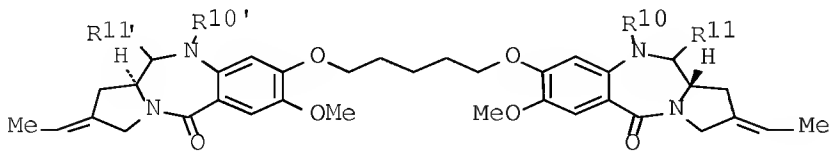
	EP 1723152	A1	20061122	EP 2005-717979	20050309
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	JP 2007528383	T	20071011	JP 2007-502398	20050309
	US 2007185073	A1	20070809	US 2007-598691	20070214
PRAI	GB 2004-5319	A	20040309		
	GB 2004-12409	A	20040603		
	WO 2005-GB915	W	20050309		

OS CASREACT 143:306350; MARPAT 143:306350
GI



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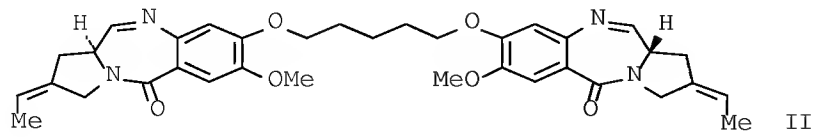
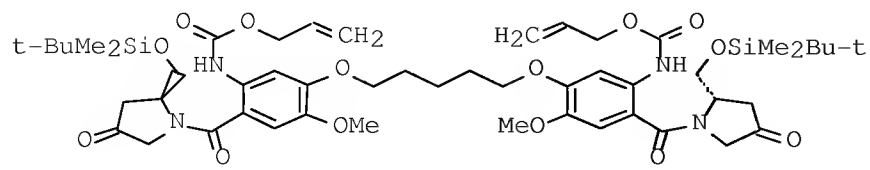


II



IV

AB Title compds. I [R10 = N-protecting group; R11 = OH, OR12; R12 = O-protecting group; or R10 and R11 together form a double bond between N10 and C11; R10' = R10; R11' = R11; and their geometrical isomers, salts and solvates] were prepared for use in the manufacture of a medicament for treating gene-based diseases, such as proliferative, and infections by Gram-pos. bacteria. For example, Z-, Z- isomer of II (III) was prepared, in 4 steps, by Wittig reaction of bis-ketone IV with ethyltriphenylphosphonium bromide, tert-butyldimethylsilyl-deprotection, cyclization, and allyloxycarbonyl-deprotection. Pyrrolobenzodiazepine dimer III displayed antitumor potency (IC50 0.05 nM) against K562 human chronic myeloid leukemia cells and crosslinking reactivity (XL50 = 2.7±1.6 nM). Pyrrolobenzodiazepine dimer III showed activity against Gram-pos. bacteria; for example the MIC90 values for III were 0.03 against methicillin resistant Staphylococcus aureus, 0.06 mg/L against vancomycin resistant enterococci and Listeria monoocytogenes, and 0.015 mg/L against Streptococcus pyogenes and Streptococcus agalactiae.

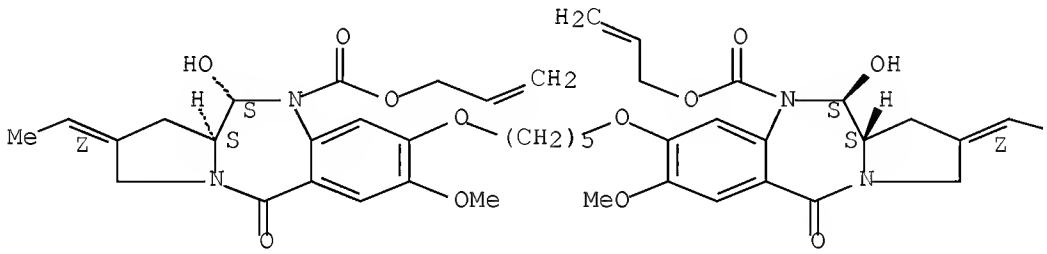
IT 864528-73-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of pyrrolobenzodiazepine dimers as antiproliferative and antibacterial agents)

RN 864528-73-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2-ethylidene-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (2Z,2'Z,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1004754 CAPLUS Full-text
DN 143:306349
TI Preparation, DNA crosslinking reactivity and antiproliferative activity of pyrrolobenzodiazepine dimers
IN Howard, Philip Wilson; Kang, Gyoung-Dong
PA Spirogen Limited, UK
SO PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005085259	A2	20050915	WO 2005-GB770	20050301
	WO 2005085259	A3	20060105		
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	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1723151	A2	20061122	EP 2005-717848	20050301
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	IN 2006DN04922	A	20070817	IN 2006-DN4922	20060825
	US 2007191309	A1	20070816	US 2007-598482	20070206
PRAI	GB 2004-4577	A	20040301		
	WO 2005-GB770	W	20050301		

OS CASREACT 143:306349; MARPAT 143:306349
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R2, R3 = independently H, :O, :CH2, CN, R, OR, halo, etc.; R6, R9 = independently H, R, OH, OR, NRR', SH, etc.; R, R' = independently (un)substituted alkyl, heterocyclyl, aryl; when X = RA, Y = OH or A-R''-A'-PDB; when X = OH or A-R''-A'-PDB, Y = RA; RA = H, R, OR, NO2, etc.; A, A' = independently O, S, NH; R'' = alkylene, optionally interrupted by one or more O, S, NH and/or aryl rings; PDB = pyrrolobenzodiazepine; R10 = carbamate-based N protecting group; R11 = O protecting group; or R10 and R11 together form a double bond between N10 and C11; and their salts, solvates, and chemical protected forms] were prepared for the manufacture of a medicament for treating a proliferative disease. Thus, reacting pyrrolobenzodiazepine (PBD) monomer II with 1,5-diiodopentane, followed by deprotection/dehydration gave PBD dimer III. PBD dimer III displayed antitumor potency (IC50 = 0.5 μM) against K562 human chronic myeloid leukemia cells DNA crosslinking reactivity (XL50 = 0.07 μM).

IT 864665-75-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

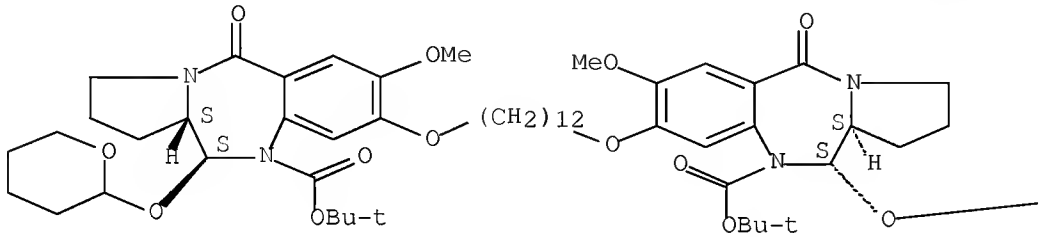
(drug candidate; preparation, DNA crosslinking reactivity and cytotoxicity of pyrrolobenzodiazepines)

RN 864665-75-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,12-dodecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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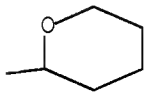

IT 864665-37-2P 864665-39-4P 864665-41-8P
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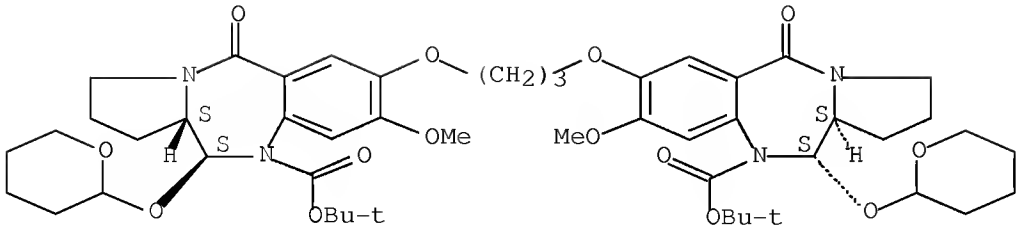
864665-55-4P 864665-61-2P 864665-62-3P
864665-63-4P 864665-64-5P 864665-65-6P
864665-67-8P 864665-69-0P 864665-71-4P
864665-73-6P 864665-85-0P 864665-87-2P
864665-89-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation, DNA crosslinking reactivity and cytotoxicity of pyrrolobenzodiazepines)

RN 864665-37-2 CAPLUS

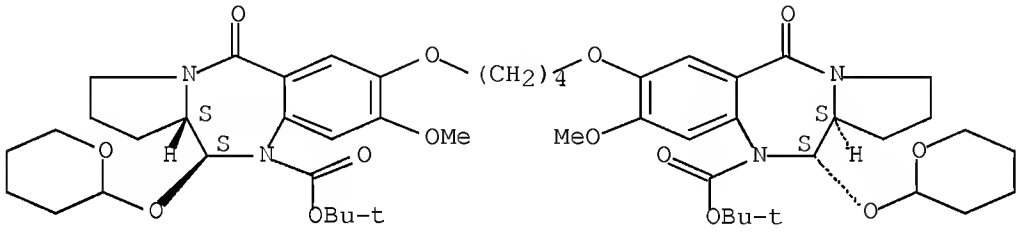
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



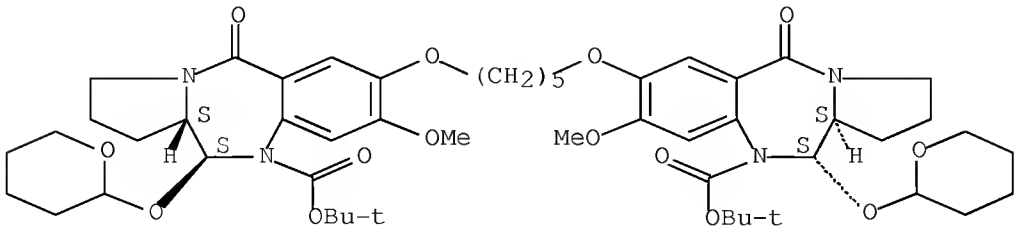
RN 864665-39-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,4-butanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



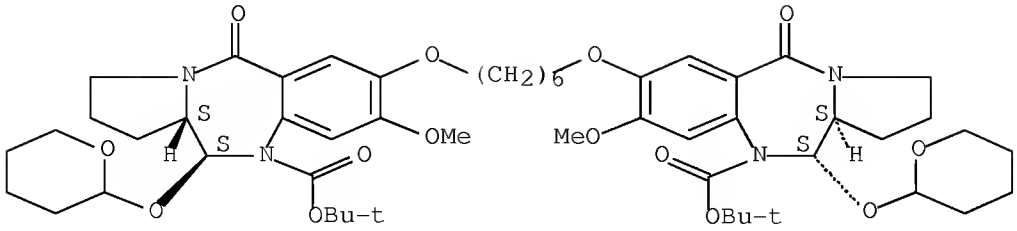
RN 864665-41-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,5-pentanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



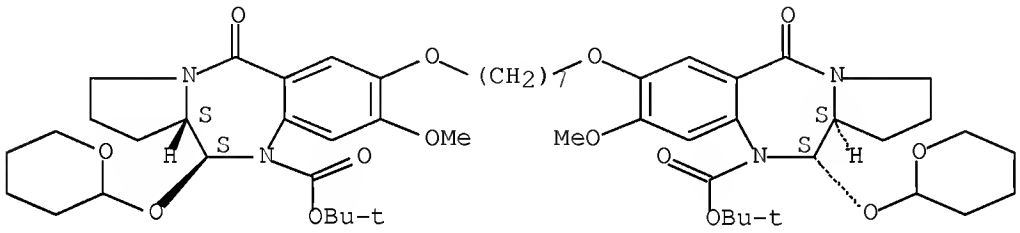
RN 864665-43-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,6-hexanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



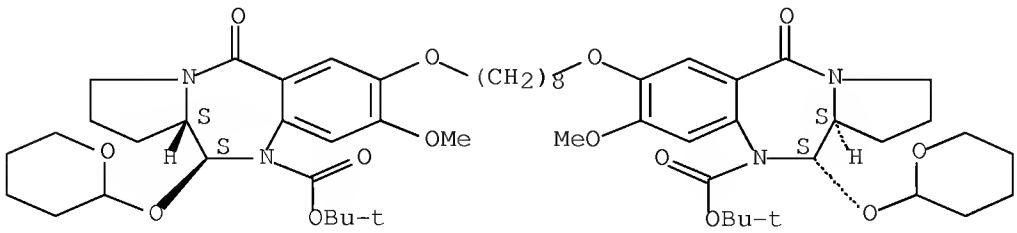
RN 864665-45-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,7-heptanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 864665-47-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,8-octanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

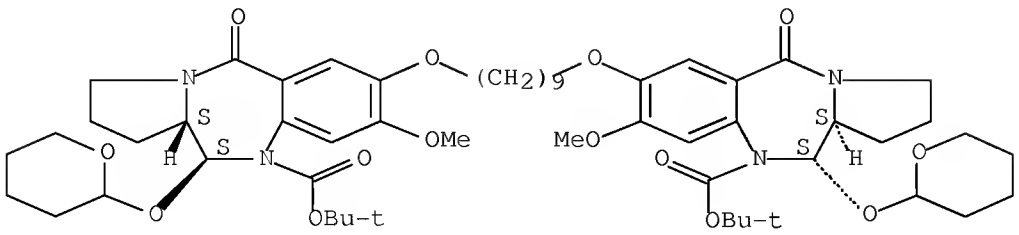
Absolute stereochemistry.



RN 864665-49-6 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,9-nonanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester,

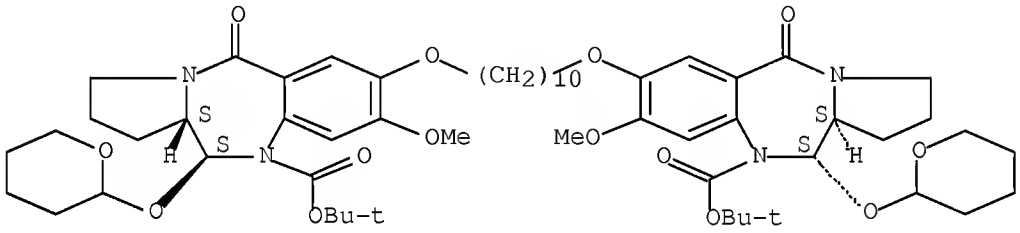
(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



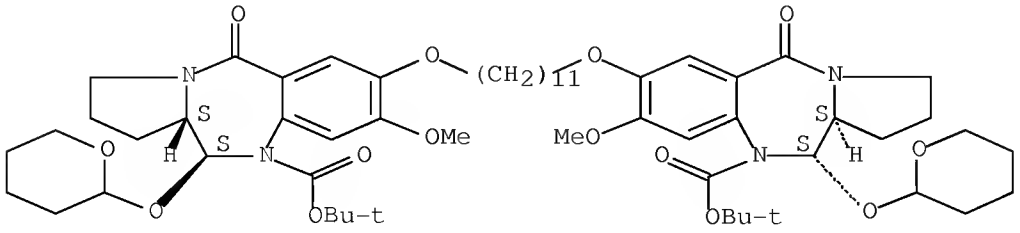
RN 864665-51-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,10-decanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 864665-53-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 7,7'-[1,11-undecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

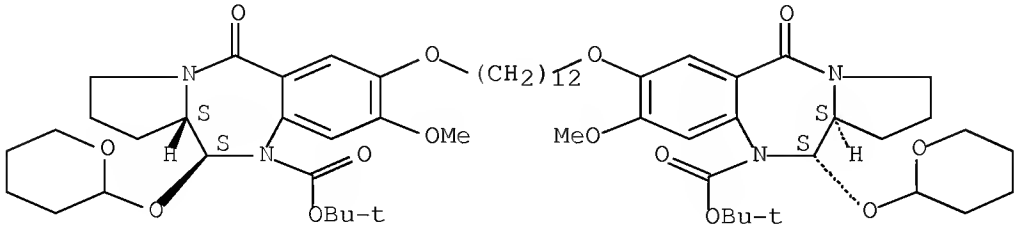
Absolute stereochemistry.



RN 864665-55-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid,

7,7'-[1,12-dodecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-8-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

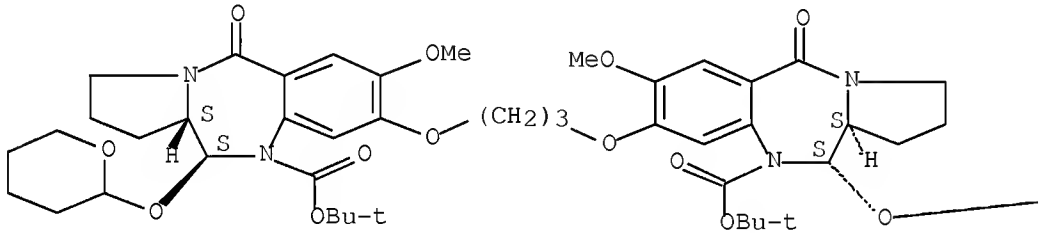
Absolute stereochemistry.



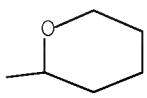
RN 864665-61-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



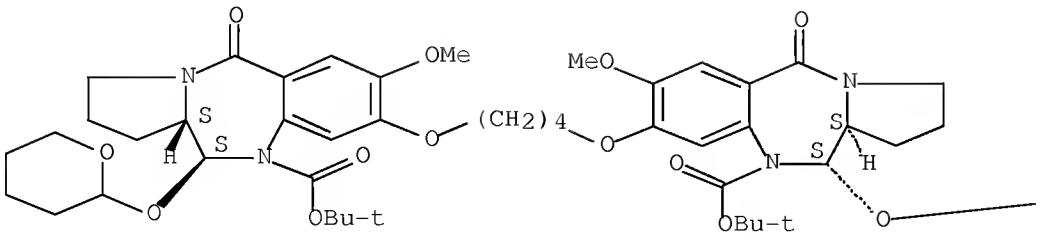
PAGE 1-B



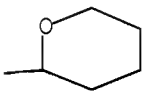
RN 864665-62-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,4-butanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



RN 864665-63-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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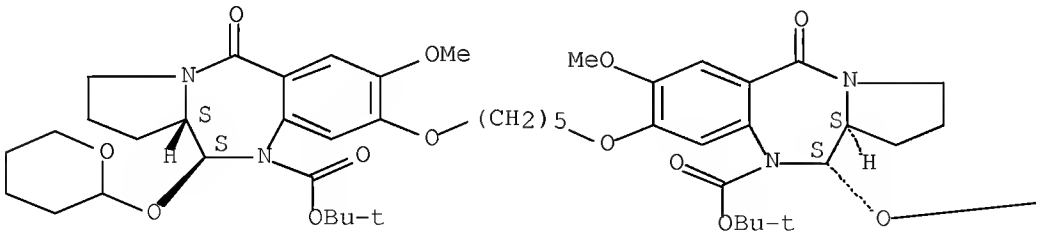

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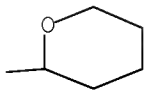

RN 864665-64-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,6-hexanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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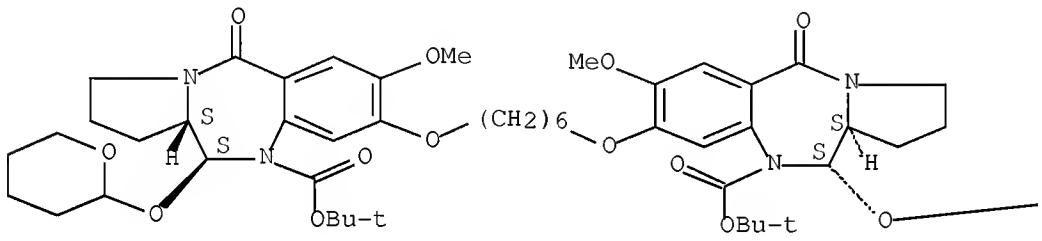
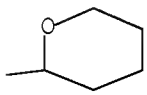


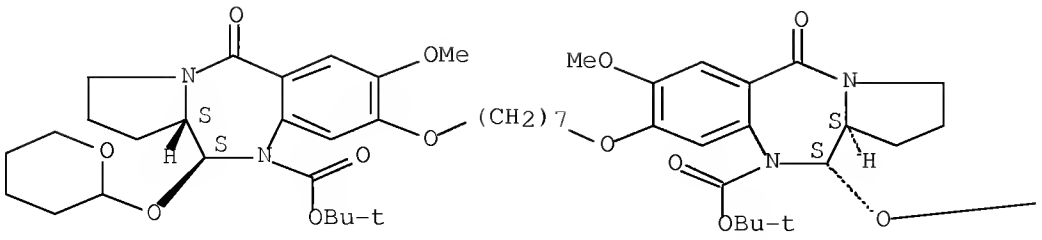
PAGE 1-B



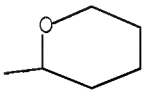
RN 864665-65-6 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,7-heptanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



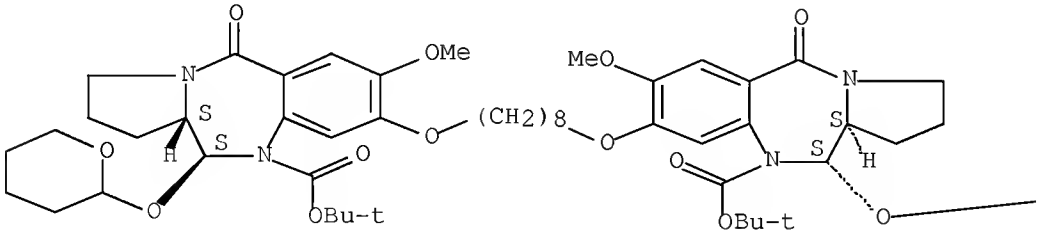
PAGE 1-B



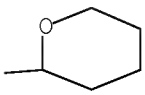
RN 864665-67-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,8-octanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



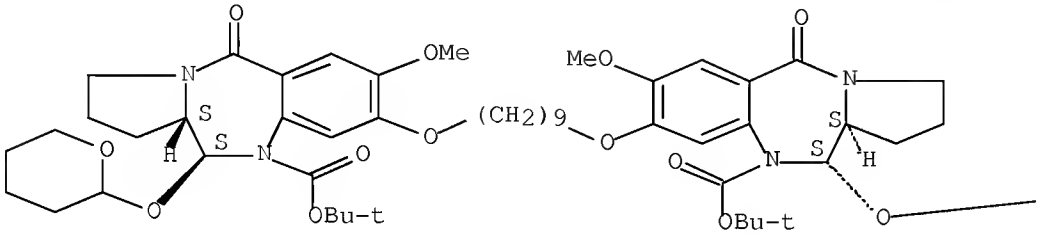
PAGE 1-B



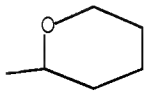
RN 864665-69-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,9-nonanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



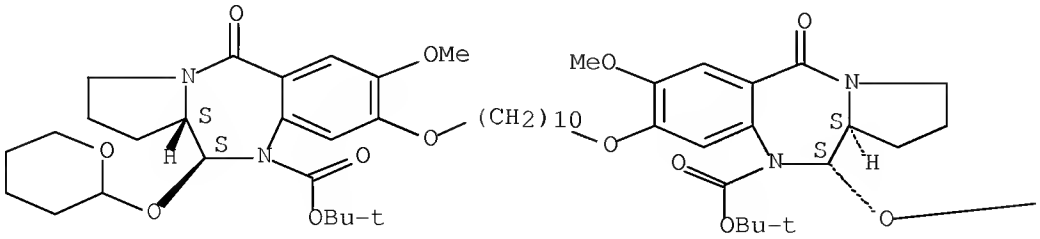
PAGE 1-B



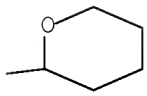
RN 864665-71-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,10-decanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



RN 864665-73-6 CAPLUS
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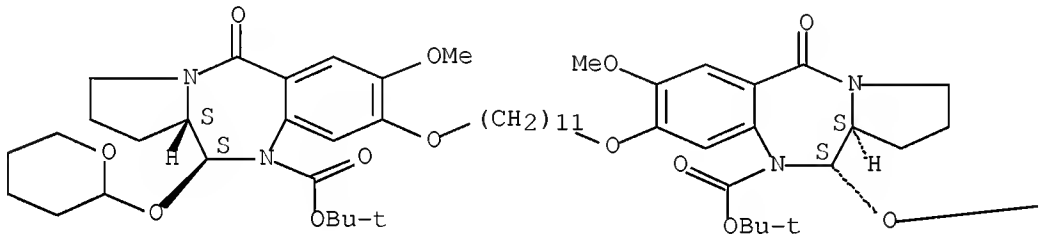
Absolute stereochemistry.

PAGE 1-A



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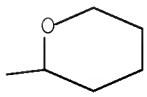
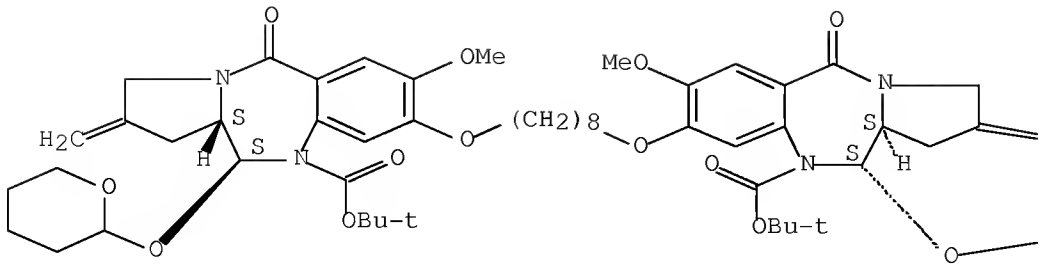


RN 864665-85-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,8-octanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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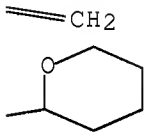
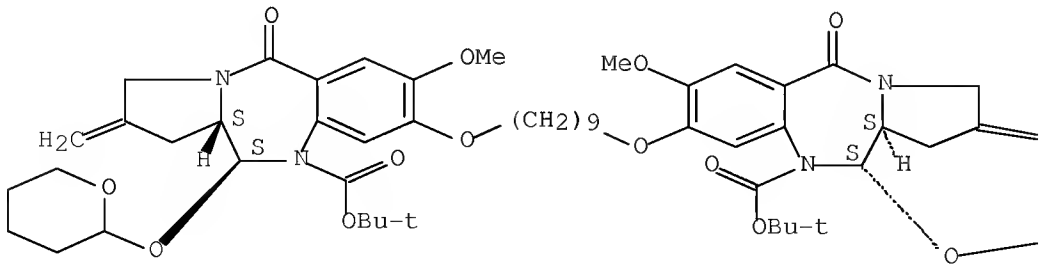


RN 864665-87-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,9-undecanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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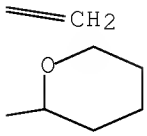

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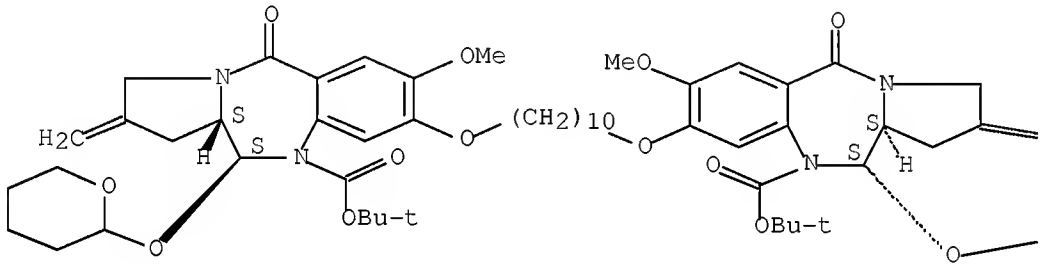
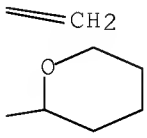
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,10-decanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-methylene-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, bis(1,1-dimethylethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L5 ANSWER 6 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1004748 CAPLUS Full-text
DN 143:306348
TI Preparation of pyrrolobenzodiazepinone derivatives as antitumor agents
IN Howard, Philip Wilson; Gregson, Stephen John
PA Spirogen Limited, UK
SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005085251	A1	20050915	WO 2005-GB768	20050301
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2005219626	A1	20050915	AU 2005-219626	20050301
	CA 2558195	A1	20050915	CA 2005-2558195	20050301
	EP 1720881	A1	20061115	EP 2005-717846	20050301
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	JP 2007525535	T	20070906	JP 2007-501340	20050301
	US 2007173497	A1	20070726	US 2007-598518	20070206
PRAI	GB 2004-4575	A	20040301		
	GB 2004-26392	A	20041201		
	WO 2005-GB768	W	20050301		

OS CASREACT 143:306348; MARPAT 143:306348
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = labile leaving group, alkenyl or substituted phenyl; R2 and R5 independently = H, OH, SH, etc.; R3 and R4 independently = H, NH2, halo, etc. or the compound is a dimer with each monomer being of formula I, where the R3 and R4 groups of each monomer form together a dimer bridge -X-R-X-; R = alkylene group, which may be interrupted by heteroatoms or aromatic rings; X = O, S or NH; R6 = carbamate-based N-protecting group; R7 = oxygen protecting group or OH or R6 and R7 together form double bond between N10 and C11] and their pharmaceutically acceptable salts, are prepared and disclosed as antitumor agents. Thus, e.g., II was prepared by palladium catalyzed coupling of III (preparation given) with trans-propenylboronic acid followed by deprotection. The in vitro cytotoxicity of I towards K562 human chronic myeloid leukemia cells was evaluated using ELISA assay and it was revealed that selected compds. of the invention displayed IC50 values of less than 1 μM. I should prove useful in the treatment of proliferative diseases such as leukemia. Pharmaceutical compns. comprising I are disclosed.

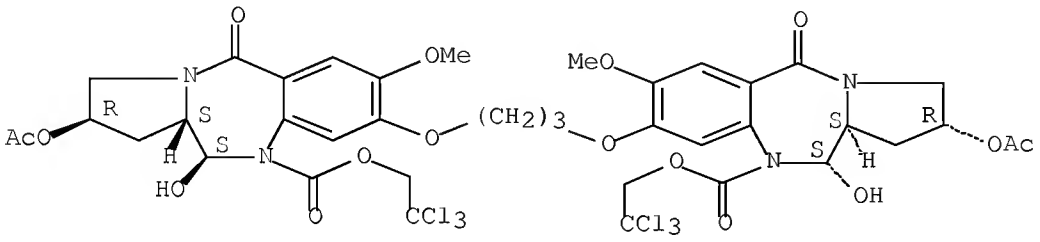
IT 864755-08-8P 864755-09-9P 864755-10-2P
864755-11-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrrolobenzodiazepinone derivs. as antitumor agents)

RN 864755-08-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

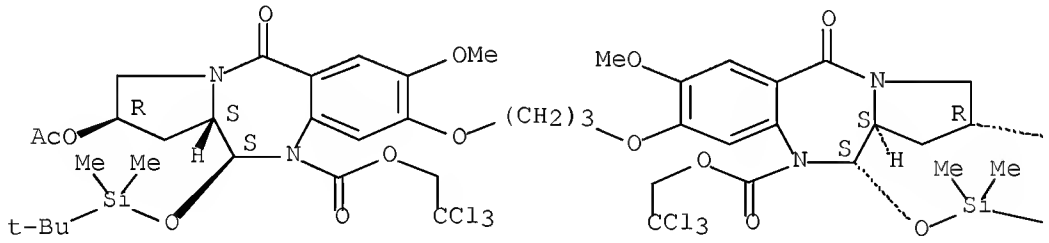


RN 864755-09-9 CAPLUS

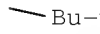
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2-(acetyloxy)-11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

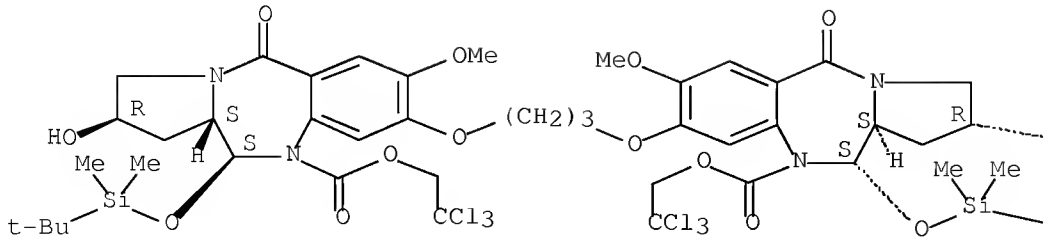


RN 864755-10-2 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-2-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (2R,2'R,11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

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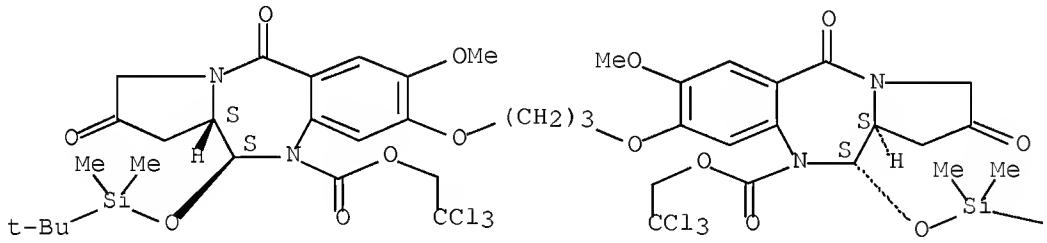
RN 864755-11-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,11,11a-tetrahydro-7-methoxy-2,5-dioxo-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

—Bu-t

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1004747 CAPLUS Full-text
DN 143:306347
TI Preparation of C8/C8' linked 5-oxo-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c]-1,4-benzodiazepine dimers with 1H-pyrrole-dicarboxylic acid amide linkers and oligomeric analogs thereof as well as related compounds for the treatment of proliferative diseases
IN Howard, Philip Wilson; Gregson, Stephen John; Tiberghien, Arnaud Charles
PA Spirogen Limited, UK
SO PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005085250	A1	20050915	WO 2005-GB767	20050301
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1720880	A1	20061115	EP 2005-717845	20050301
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	US 2007191349	A1	20070816	US 2007-598470	20070206
PRAI	GB 2004-4578	A	20040301		
	WO 2005-GB767	W	20050301		

OS CASREACT 143:306347; MARPAT 143:306347
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [Z = AYX(Het)naL(Het)nbL(Het)ncT(Het')ndL(Het')neL(Het')nf X'Y'A'; A = O, S, NH, or bond; Y = divalent group or single bond; X and X' are both either NH or CO; Het and Het' independently = aminoheteroarylenecarbonyl; each L independently = β-alanine, glycine, 4-aminobutanoic acid or single bond; T = divalent linker group; A', Y' are independently selected definitions for A and Y; na, mb, mc, nd, ne, nf independently = 0-5 with their sum = 0-16; R2 and R3 = H, OH, CN, etc.; R6, R7 and R9 independently = H, SH, NH2, NO2, etc.; R10 = N-protecting group; R15 = OH, =O, =S, OR where R = protecting group; R10 and R15 may together form a double bond between atoms to which they are attached], and their pharmaceutically acceptable salts, are prepared and disclosed as antiproliferative agents. Thus, e.g., II was prepared by bischlorination of N-methyl-2,5-pyrroledicarboxylic acid followed by bisamidation with aniline III and removal of N-protecting group. I were evaluated for DNA crosslinking ability, in vitro cytotoxicity in human chromic myeloid leukemia cells and screened against 60 human tumor cell lines. For example, compound II demon stated an IC50 of 1.2 μM in in vitro cytotoxicity assay and a GI50 of 1.0 μM in tumor cell screening. Further aspects of the

present invention relate to their use in the manufacture of a medicament for the treatment of a proliferative disease.

IT 864767-70-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

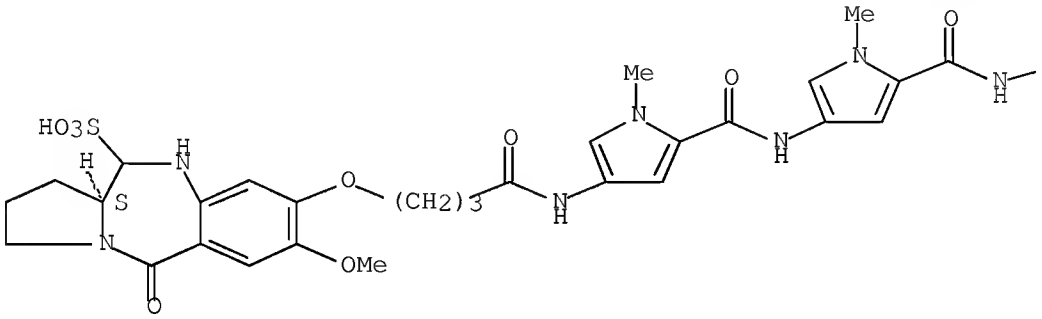
(drug candidate; preparation of oxotetrahydropyrrolobenzodiazepine dimers containing pyrroledicarboxylic acid amide linkers and oligomeric analogs thereof as antiproliferative agents)

RN 864767-70-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid, 8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,5,10,11,11a-hexahydro-7-methoxy-5-oxo-, disodium salt, (11aS,11'aS)- (9CI) (CA INDEX NAME)

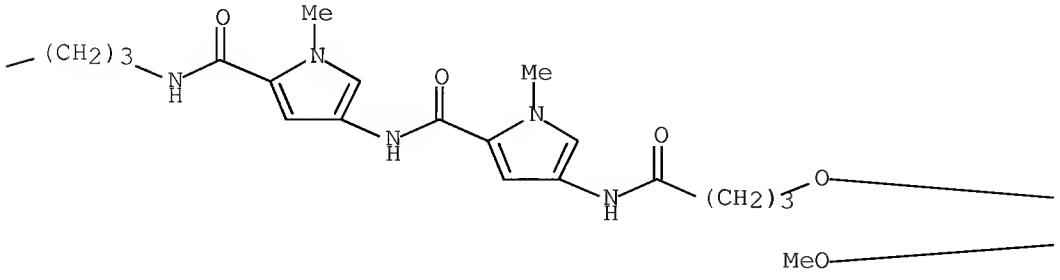
Absolute stereochemistry.

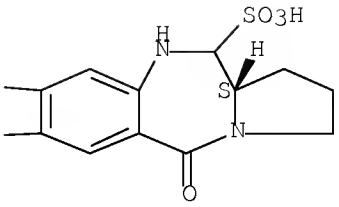
PAGE 1-A



●2 Na

PAGE 1-B



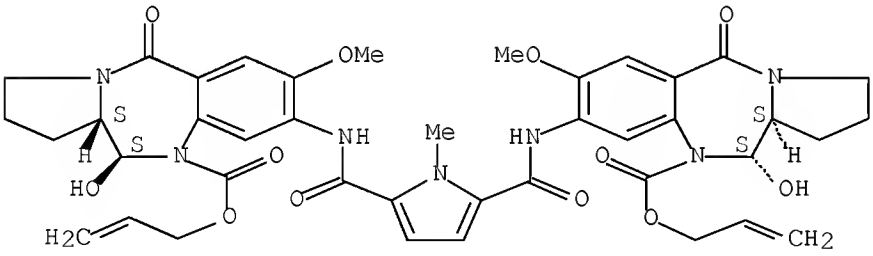


IT 864672-61-7P 864672-62-8P 864672-68-4P
864672-70-8P 864672-73-1P 864672-75-3P
864672-77-5P 864672-83-3P 864672-90-2P
864672-92-4P 864672-96-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of oxotetrahydropyrrolobenzodiazepine dimers containing pyrroledicarboxylic acid amide linkers and oligomeric analogs thereof as antiproliferative agents)

RN 864672-61-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[(1-methyl-1H-pyrrole-2,5-diyl)bis(carbonylimino)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

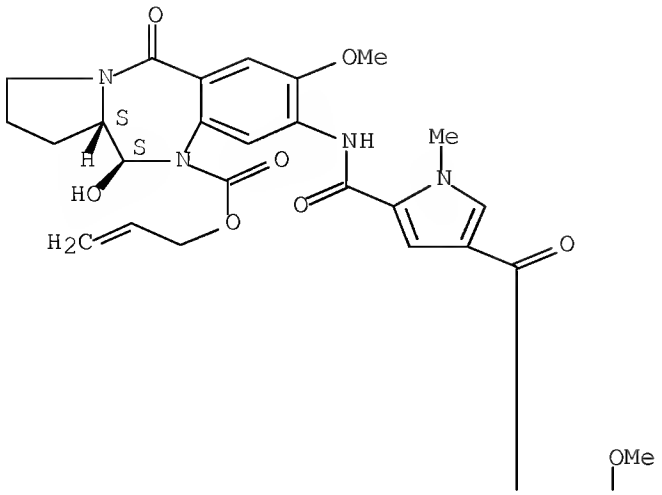


RN 864672-62-8 CAPLUS

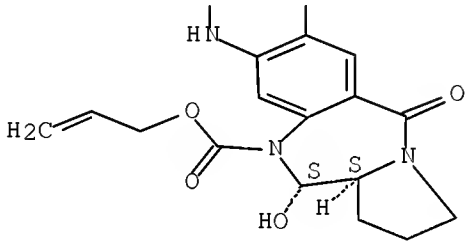
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[(1-methyl-1H-pyrrole-2,4-diyl)bis(carbonylimino)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



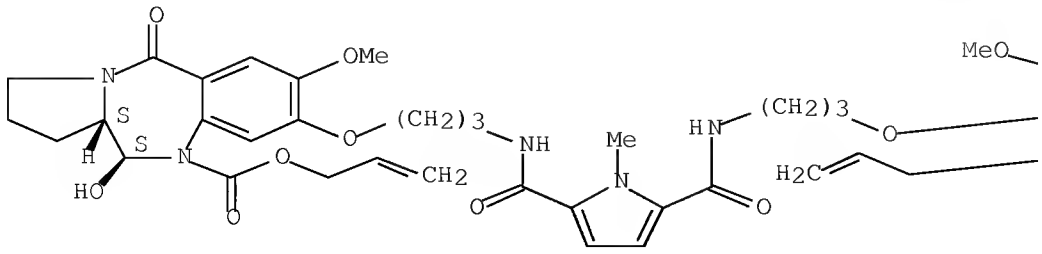
PAGE 2-A



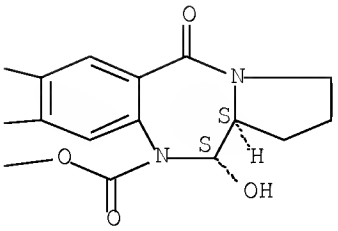
RN 864672-68-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[(1-methyl-1H-pyrrole-2,5-diyl)bis(carbonylimino-3,1-propanediyloxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

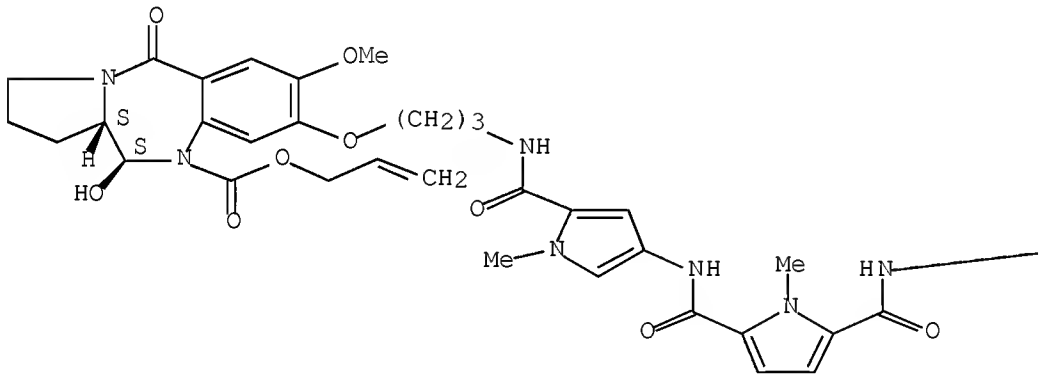


RN 864672-70-8 CAPLUS

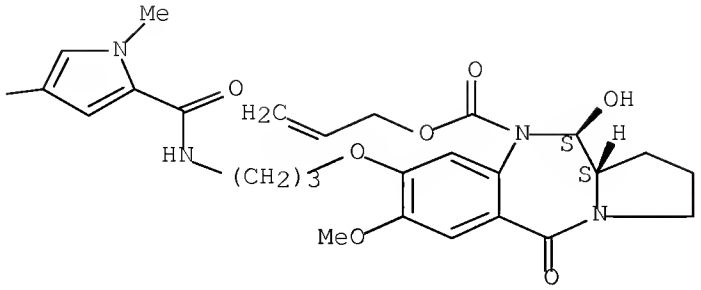
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[(1-methyl-1H-pyrrole-2,5-diyl)bis[carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)carbonylimino-3,1-propanediyloxy]]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



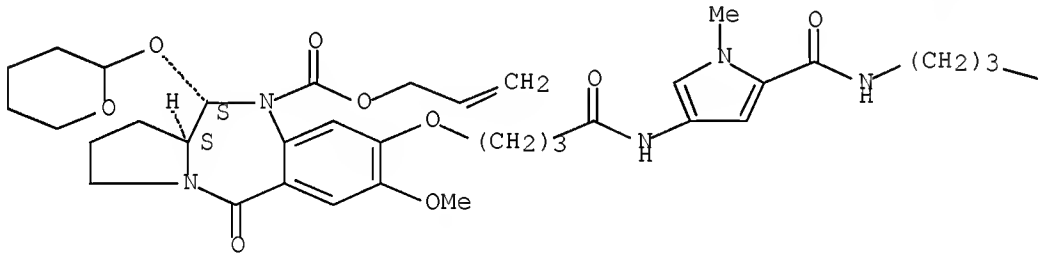
PAGE 1-B



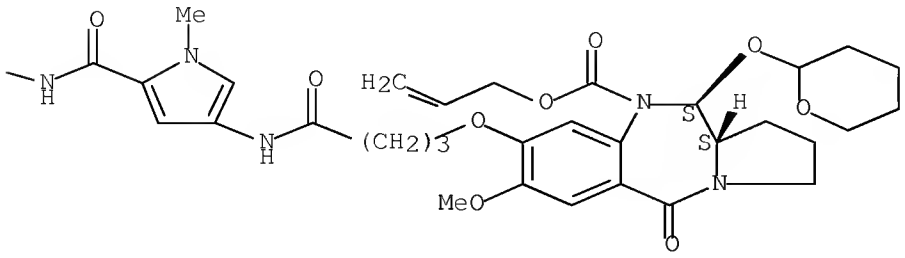
RN 864672-73-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

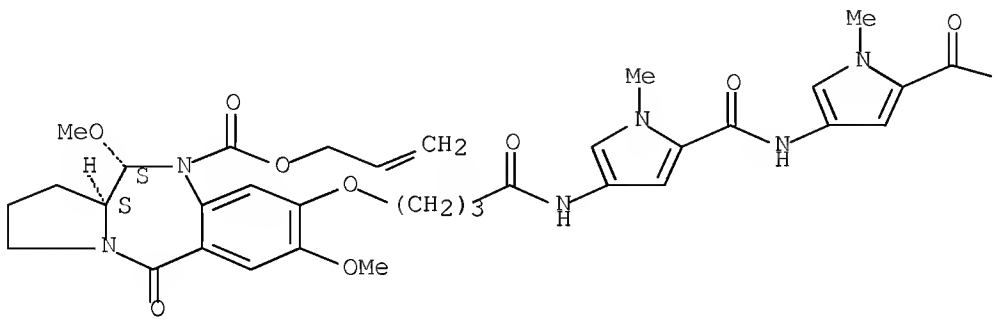


RN 864672-75-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7,11-dimethoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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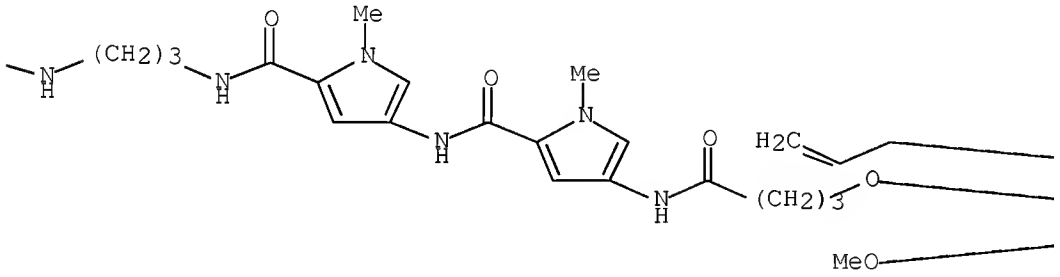
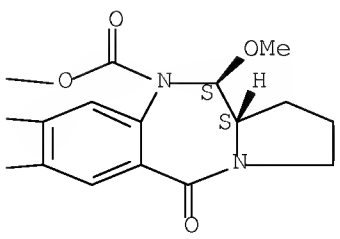


PAGE 1-C

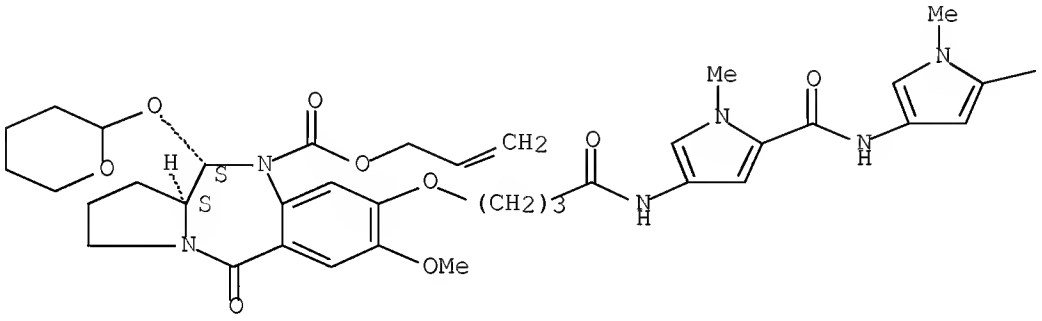


RN 864672-77-5 CAPLUS

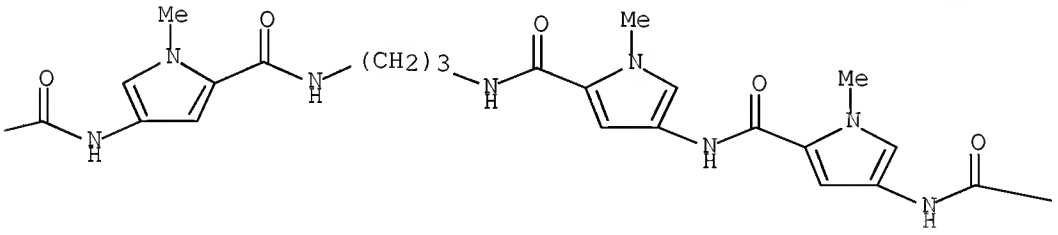
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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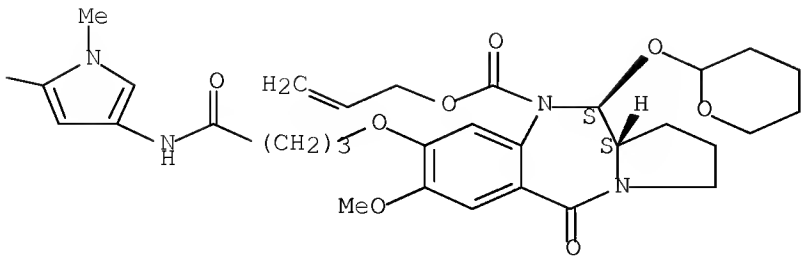
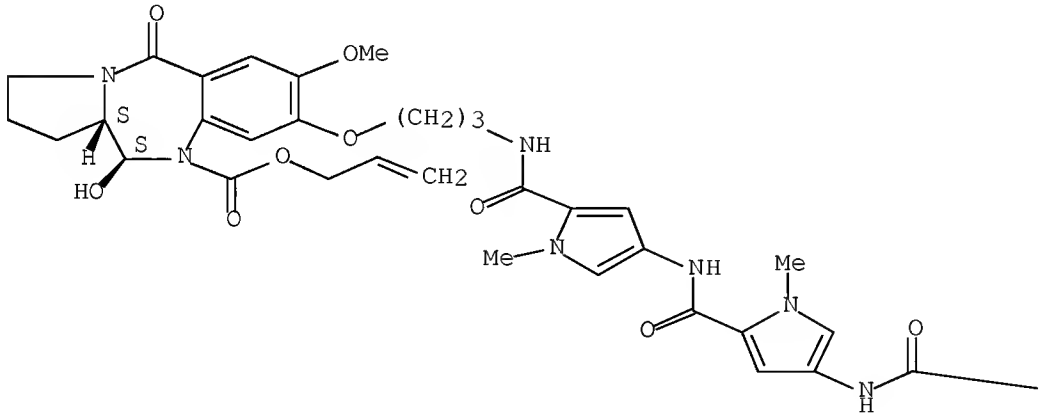


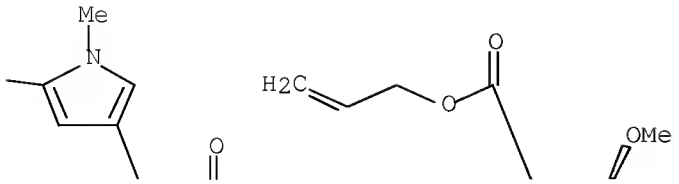
RN 864672-83-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10-carboxylic acid, 8-[3-[[[4-[[[4-[[[4-[[4-[[(11S,11aS)-2,3,5,10,11,11a-hexahydro-7,11-dimethoxy-5-oxo-10-[(2-propenyloxy)carbonyl]-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-1-oxobutyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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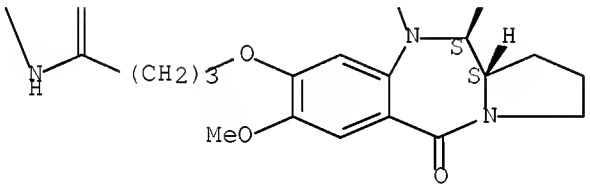
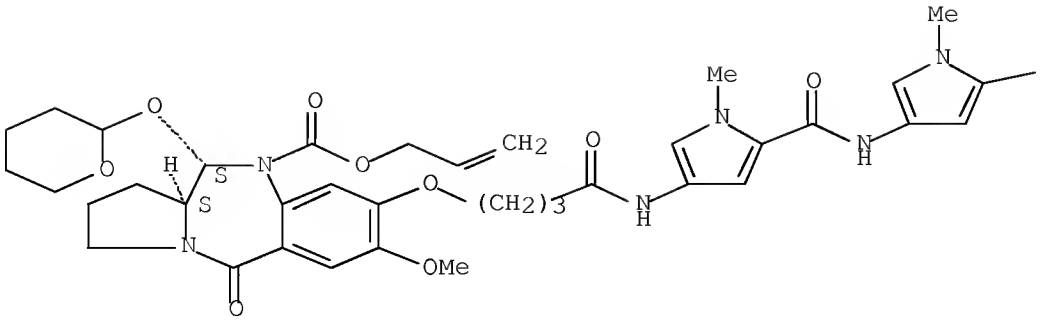


RN 864672-90-2 CAPLUS

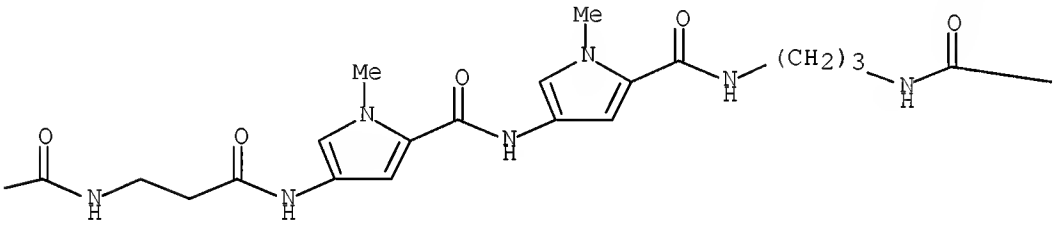
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(3-oxo-3,1-propanediyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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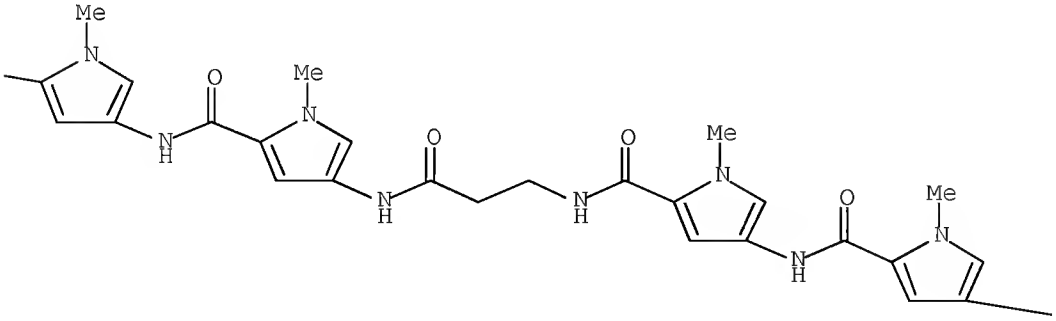

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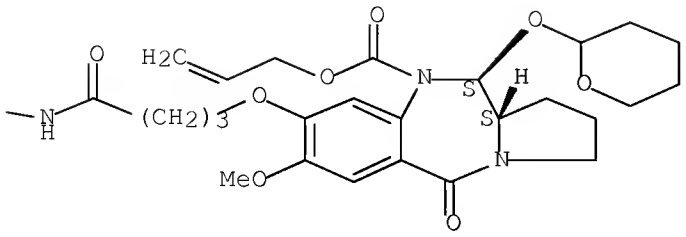
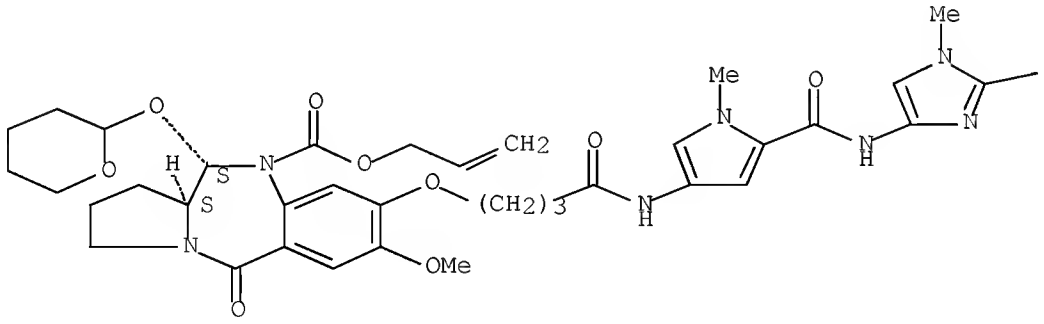


RN 864672-92-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis[iminocarbonyl(1-methyl-1H-imidazole-2,4-diyl)iminocarbonyl(1-methyl-1H-pyrrole-2,4-diyl)imino(4-oxo-4,1-butanediyl)oxy]]bis[2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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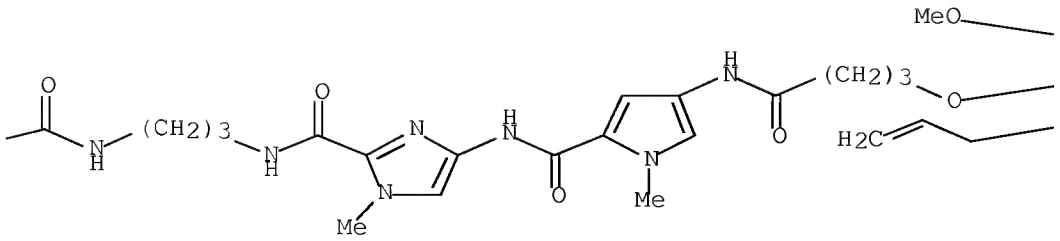
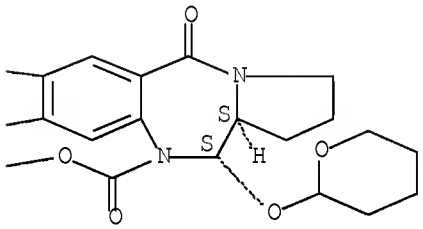


PAGE 1-C

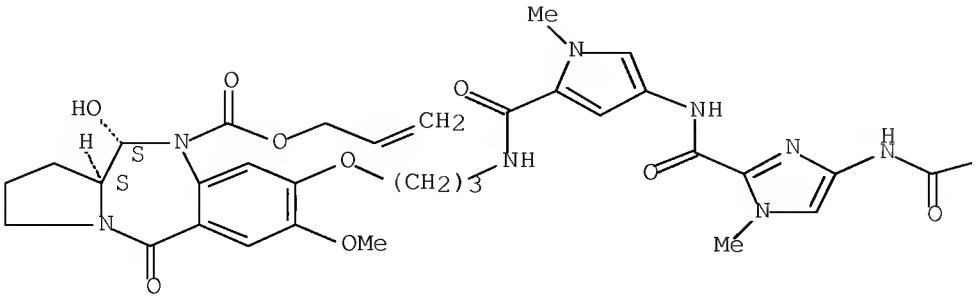


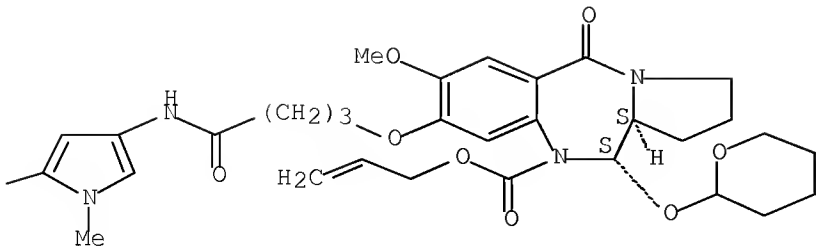
RN 864672-96-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[4-[[5-[[[2-[[[5-[[[3-[[(11S,11aS)-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-10-[(2-propenyloxy)carbonyl]-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-imidazol-4-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutoxy]-2,3,11,11a-tetrahydro-7-methoxy-5-oxo-11-[(tetrahydro-2H-pyran-2-yl)oxy]-, 2-propenyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

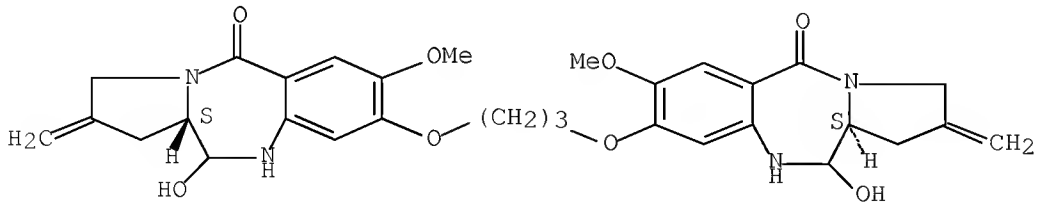




RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

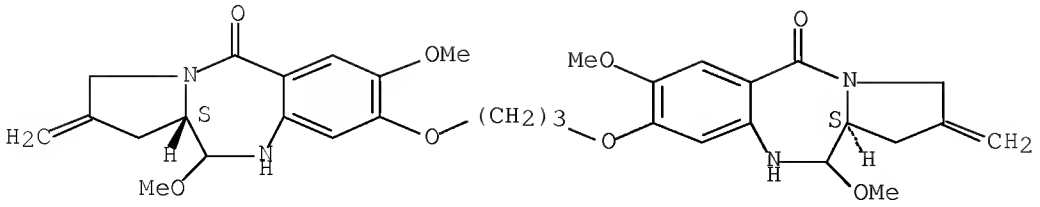
L5 ANSWER 8 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:647488 CAPLUS Full-text
DN 143:292707
TI Direct liquid chromatography determination of the reactive imine SJG-136 (NSC 694501)
AU Cheung, Andrew; Struble, Elaine; He, Jingyi; Yang, Chun; Wang, Euphemia; Thurston, David E.; Liu, Paul
CS Analytical Chemistry Department, SRI International, Menlo Park, CA, 94025, USA
SO Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2005), 822(1-2), 10-20
CODEN: JCBAAI; ISSN: 1570-0232
PB Elsevier B.V.
DT Journal
LA English
AB SJG-136 (NSC 694501), 8,8'-[[(propane-1,3-diyl)dioxy]bis[(11aS)-7-methoxy- 2-methylidene-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4] benzodiazepin-5-one]], which is being developed as a DNA-interactive antitumor agent, contains highly reactive imines in the diazepinone portions of the mol. Water or alc. adds readily to the imino moiety to form the corresponding carbinolamine or its alkyl ether, resp. This sensitivity to protic substances poses a formidable challenge to the formulation and HPLC assay development for the compound After studying the solution chemical of SJG-136 and its potential interaction with various stationary phases, two reversed-phase liquid chromatog. assays for the compound have been developed. A direct assay that separates SJG-136 from its water or methanol adducts and an indirect assay that quantifies SJG-136 as its dihydrate adduct are reported. The latter method, which is more practical for drug development, has been validated. It is reproducible (R.S.D. < 2%), linear (r 2 = 0.9999) and accurate (within 98-102% recovery), with a lower detection limit of 2.5 ng.
IT 851177-99-6 851178-00-2
RL: FMU (Formation, unclassified); PRP (Properties); FORM (Formation, nonpreparative)
(direct liquid chromatog. determination of the reactive imine SJG-136)
RN 851177-99-6 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-11-hydroxy-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 851178-00-2 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7,11-dimethoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:409522 CAPLUS Full-text
DN 142:463770
TI Preparation, DNA crosslinking reactivity and antitumor activity of pyrrolobenzodiazepines
IN Howard, Philip Wilson; Thurston, David Edwin; Gregson, Stephen John
PA Spirogen Limited, UK
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005042535	A1	20050512	WO 2004-GB4497	20041022
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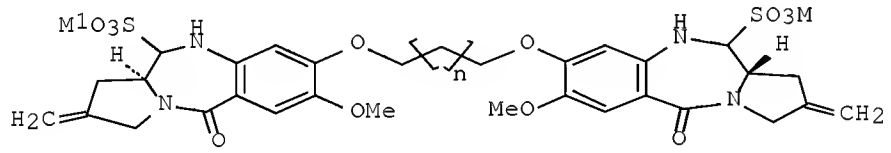
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2006270661	A1	20061130	US 2005-129207	20050513
	US 7244724	B2	20070717		
PRAI	US 2003-513751P	P	20031022		
	GB 2004-16511	A	20040723		
	WO 2004-GB4497	A1	20041022		

OS MARPAT 142:463770
GI



I

AB The present invention discloses preparation of pyrrolobenzodiazepine derivs., such as I [n = 1 to 10; M, M1 = monovalent pharmaceutically acceptable cation; M and M1 together = divalent pharmaceutically acceptable cation], or solvate thereof, in the manufacture of a medicament for the treatment of a gene-based disease. Thus, I [n = 1; M, M1 = Na (II)] prepared by adding an aqueous solution of sodium sulfite to a stirred solution I [n = 1; M, M1 = H] in dichloromethane followed by vigorous stirring for 24 h. Pyrrolobenzodiazepine derivative II exhibited antitumor potency (IC50 less than 10 nM) against K562 human chronic myeloid leukemia cells and crosslinking reactivity [XL50 less than 50 nM].

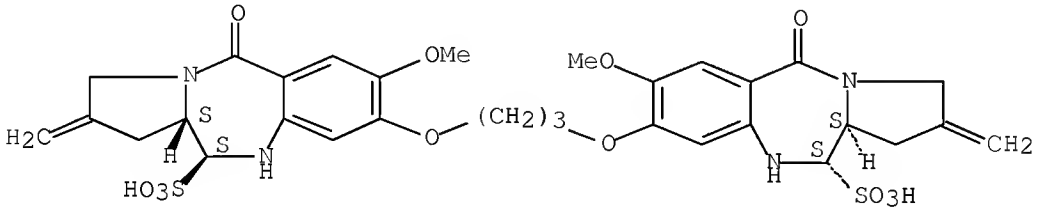
IT 851455-96-4P, SJG 720 851455-97-5P, SJG 738
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation, DNA crosslinking reactivity and cytotoxicity of

pyrrolobenzodiazepines)

RN 851455-96-4 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,5,10,11,11a-hexahydro-7-methoxy-2-methylene-5-oxo-, disodium salt, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

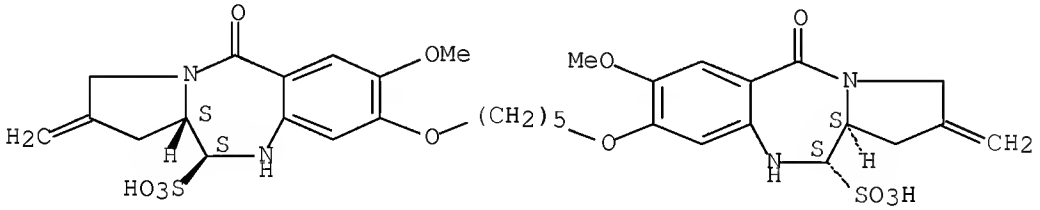


●2 Na

RN 851455-97-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-11-sulfonic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2,3,5,10,11,11a-hexahydro-7-methoxy-2-methylene-5-oxo-, disodium salt, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



●2 Na

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:395315 CAPLUS Full-text
DN 142:447059
TI Method for preparation of pyrrolobenzodiazepine derivatives and compositions comprising them
IN Vishnuvajjala, B. Rao; Liu, Paul S.; Snader, Kenneth M.; Thurston, David; Howard, Philip W.; Turner, Gregory
PA Government of the United States of America, Represented by the Secretary Department of Health and Human Services, USA; Spirogen, Ltd.; Starks Associates, Inc.; Midwest Research Institute; Hsiao, Luke Y.
SO PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005040170	A2	20050506	WO 2004-US35050	20041022
	WO 2005040170	A3	20050630		
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	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2004284075	A1	20050506	AU 2004-284075	20041022
	CA 2543318	A1	20050506	CA 2004-2543318	20041022
	EP 1675857	A2	20060705	EP 2004-817338	20041022
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
	US 2007072846	A1	20070329	US 2006-576689	20060814
PRAI	US 2003-513751P	P	20031022		
	WO 2004-US35050	W	20041022		

OS CASREACT 142:447059; MARPAT 142:447059
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Disclosed is: compds. I [X = OH, ether, silyl ether, trialkylsilyl ether, ester, carbonate, (cyclic) carbamate, (cyclic) thiocarbamate, OAc, SH, sulfide, sulfoxide, sulfone, sulfite, bisulfite, sulfonamide, amine, amide, N3, CN, halogen, triphenylphosphonium, silyl, trialkylsilyl, amino acid, phosphorus-containing group; Y = H, X; R1, R2 = H, C1-8-alkyl, aryl, heterocycle; R3, R4, R8 = H, (un)substituted C1-24-alkyl, C2-24-alkenyl, C2-24-alkynyl, (un)substituted aryl; R5, R6 = H, C1-8-alkyl, aryl, heterocycle; R7 = H, absent; T1, T2 = O, S, NR8; Z = divalent radical of (un)substituted alkane, alkene, alkyne (optionally containing a heteroatom or a carbonyl); p = ≥ 2; with the proviso that when dashed line from CY to NR7 is a double bond, R7 is absent & Y = H and with dashed line is a single bond R7 = H & Y = X; with the proviso that when the dashed line to R1 is a double bond, then R2 is absent; with the proviso that when the dashed line to R5 is a double bond, then R6 is absent] or a salt thereof, wherein the compound is a solid. Also

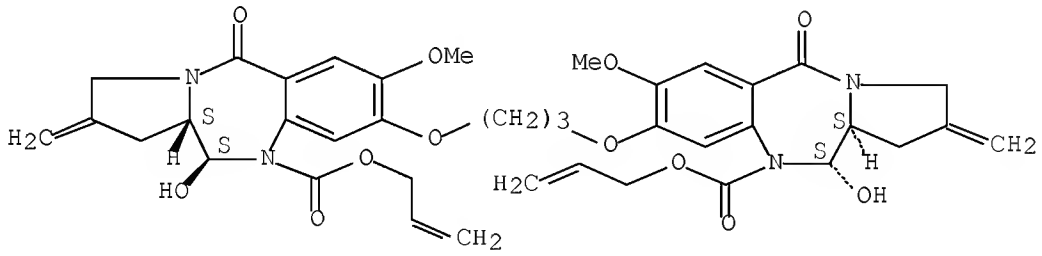
disclosed are: a pharmaceutical composition comprising a compound I and a carrier; a method of inhibiting growth of a cell, which method comprises administering in an amount effective to inhibit growth a compound I; a method of treating cancer in a mammal, which method comprises administering in an amount effective to treat cancer a compound I; a method of treating a viral, parasitic, or bacterial infection of a cell, which method comprises administering in an amount effective to treat a viral, parasitic, or bacterial infection a compound I; and a method of preparing a compound I as described herein. The method of preparation of I comprises: (a) providing a compound II ; and (b) reaction II with a nucleophile, e.g. water, an alc., a thiol or an amine, to give the crystalline solid I. Thus, dimer III [A = (CH2)3] was prepared from 4-HO-3-MeOC6H3CO2Me and trans-4-hydroxy-L-proline via coupling of diacid IV [A = (CH2)3] with trans-4-hydroxy-L-prolinol derivative V [TBDMS = SiMe2CMe3] and oxidative cyclization of bisamide VI [A = (CH2)3]. The in vitro antitumor activity of III [A = (CH2)3] was determined [LC50 = 28.2 nM vs. leukemia cell line HL-60(TB); LC50 = 67.6 nM vs. non-small cell lung cell line NCI-H23; LC50 = 251.2 nM vs. colon cell line COLO 205; LC50 = 467.7 nM vs. CNS cell line SNB-75; LC50 = 7.1 nM vs. melanoma cell line UACC-62; LC50 = 1000 nM vs. ovarian cell line SK-OV-3; LC50 = 1000 nM vs. renal cell line CAKI-1; LC50 = 1000 nM vs. prostate cell line DU-145; LC50 = 57.5 nM vs. breast cell line MDA-N].

IT 232931-64-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and N-decarbonylation of; preparation of pyrrolobenzodiazepine derivs. as antitumor antibiotics and other medicinals)

RN 232931-64-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



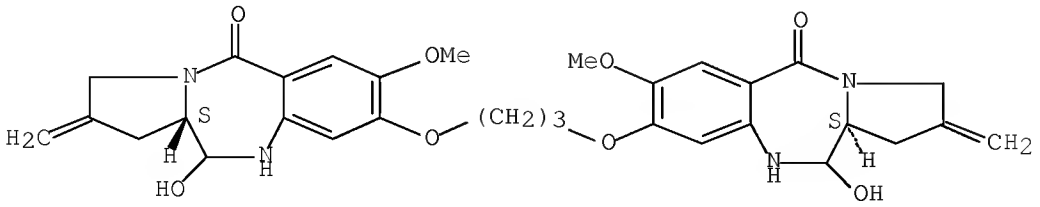
IT 851177-99-6P 851178-00-2P 851178-01-3P
851178-02-4P 851178-03-5P 851178-04-6P
851178-05-7P 851178-06-8P 851178-07-9P
851178-08-0P 851178-09-1P 851178-10-4P
851178-11-5P 851178-12-6P 851178-14-8P
851178-15-9P 851178-16-0P 851178-17-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrrolobenzodiazepine derivs. as antitumor antibiotics and other medicinals)

RN 851177-99-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-

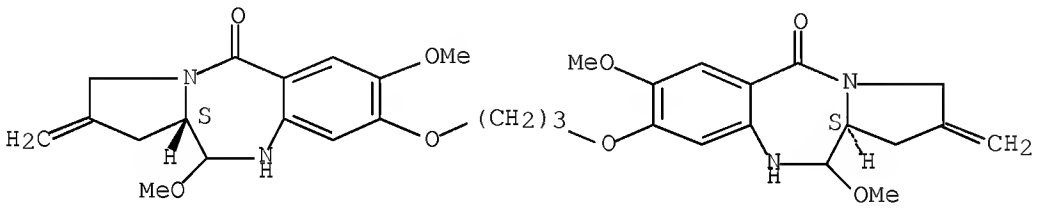
propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-11-hydroxy-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



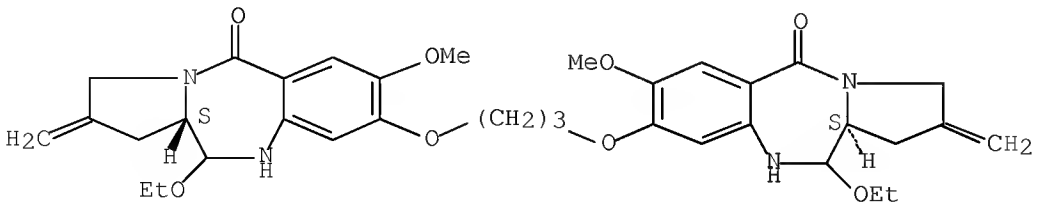
RN 851178-00-2 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7,11-dimethoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



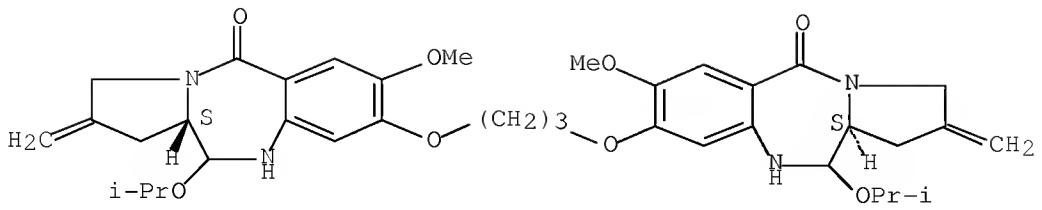
RN 851178-01-3 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[11-ethoxy-1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



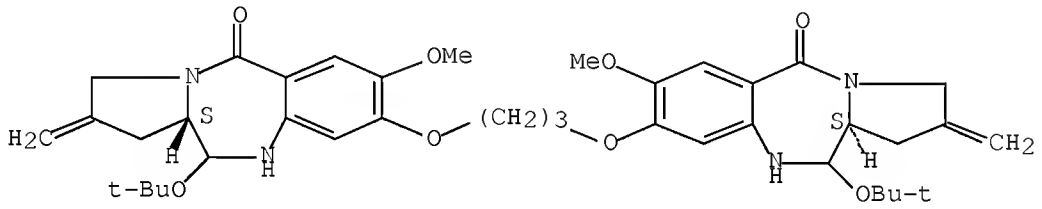
RN 851178-02-4 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-(1-methylethoxy)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



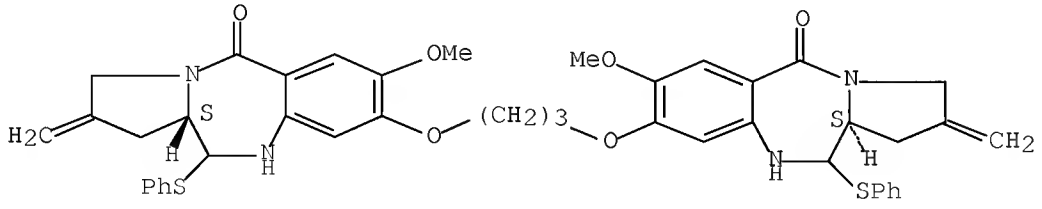
RN 851178-03-5 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[11-(1,1-dimethylethoxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 851178-04-6 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-(phenylthio)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

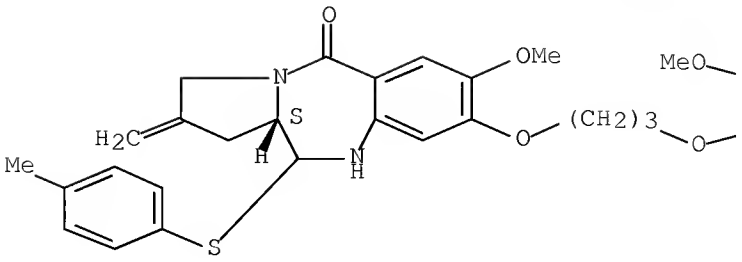
Absolute stereochemistry.



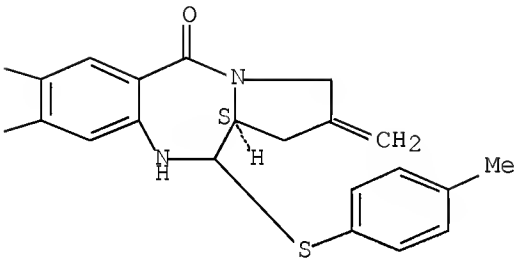
RN 851178-05-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-[(4-methylphenyl)thio]-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



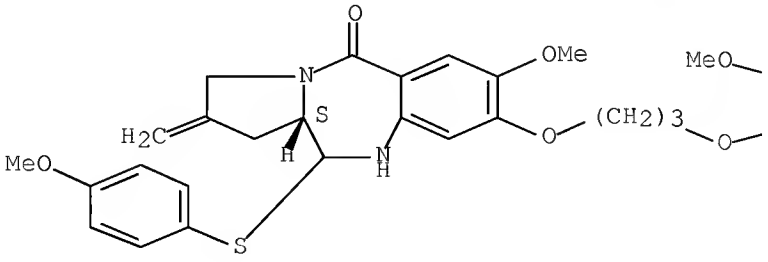
PAGE 1-B

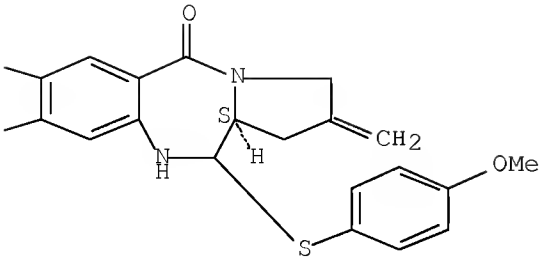


RN 851178-06-8 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-11-[(4-methoxyphenyl)thio]-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

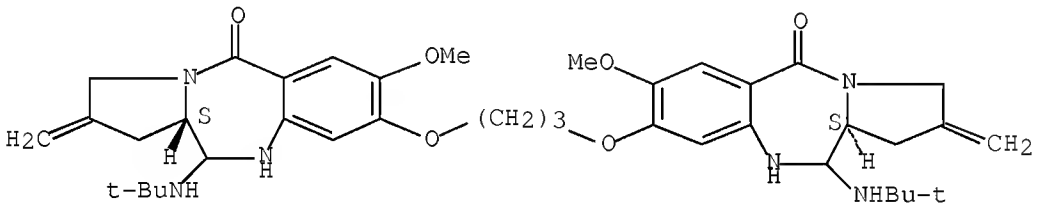
PAGE 1-A



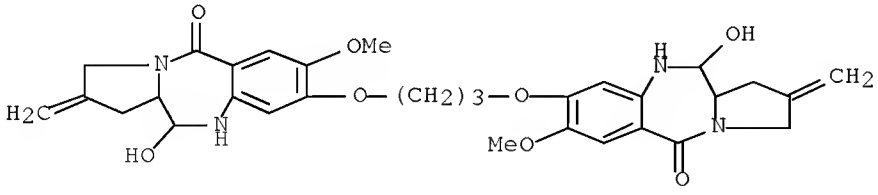


RN 851178-07-9 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[(1,1-dimethylethyl)amino]-1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

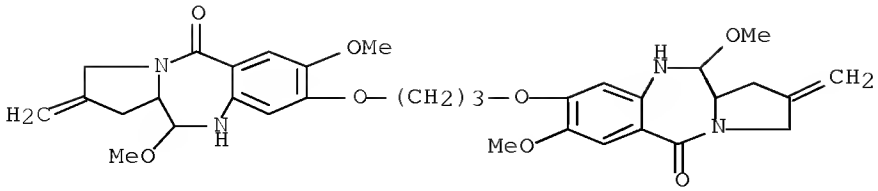
Absolute stereochemistry.



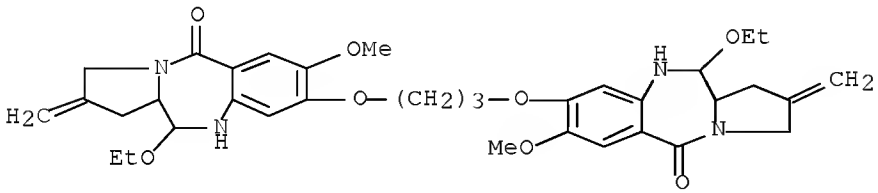
RN 851178-08-0 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-11-hydroxy-7-methoxy-2-methylene- (9CI) (CA INDEX NAME)



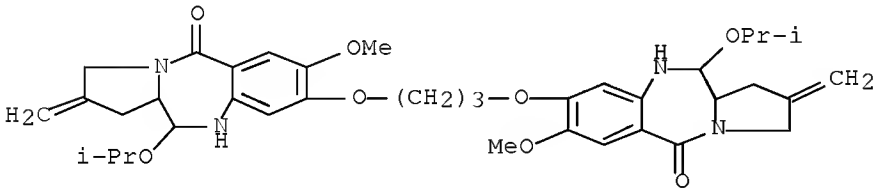
RN 851178-09-1 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7,11-dimethoxy-2-methylene- (9CI) (CA INDEX NAME)



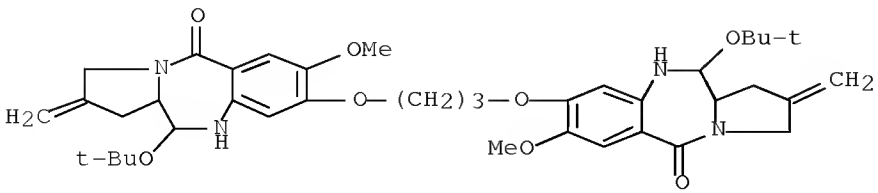
RN 851178-10-4 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[11-ethoxy-1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene- (9CI) (CA INDEX NAME)



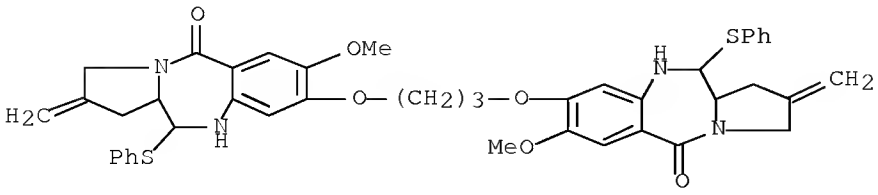
RN 851178-11-5 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-(1-methylethoxy)- (9CI) (CA INDEX NAME)



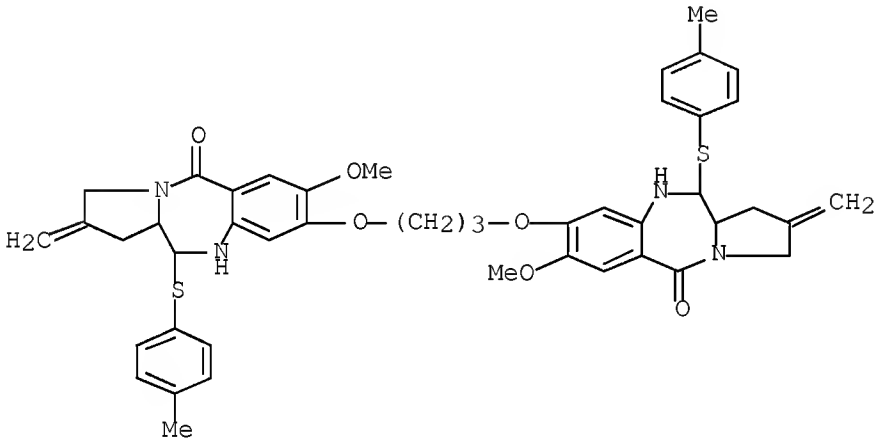
RN 851178-12-6 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[11-(1,1-dimethylethoxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene- (9CI) (CA INDEX NAME)



RN 851178-14-8 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-(phenylthio)- (9CI) (CA INDEX NAME)



RN 851178-15-9 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene-11-[(4-methylphenyl)thio]- (9CI) (CA INDEX NAME)



RN 851178-16-0 CAPLUS
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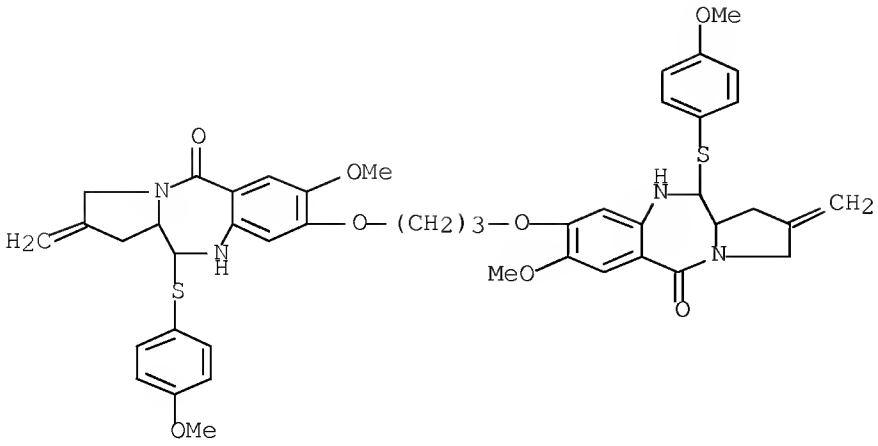
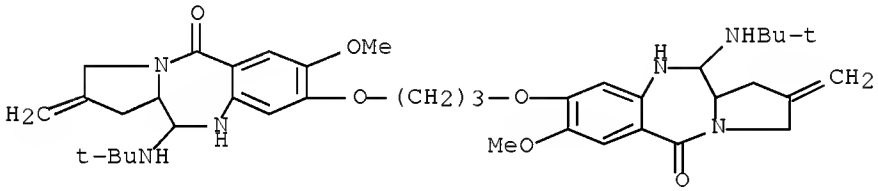


RN 851178-17-1 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[11-[(1,1-dimethylethyl)amino]-1,2,3,10,11,11a-hexahydro-7-methoxy-2-methylene- (9CI) (CA INDEX NAME)



L5 ANSWER 11 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:238991 CAPLUS Full-text
DN 142:316867
TI Synthesis of protected pyrrolobenzodiazepines
IN Howard, Philip; Masterson, Luke
PA Spirogen Limited, UK
SO PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005023814	A1	20050317	WO 2004-GB3873	20040910
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OS CASREACT 142:316867; MARPAT 142:316867
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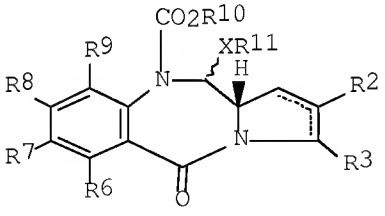

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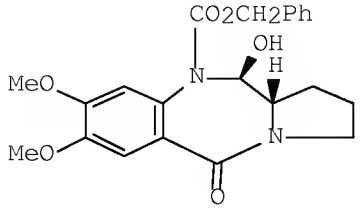


II

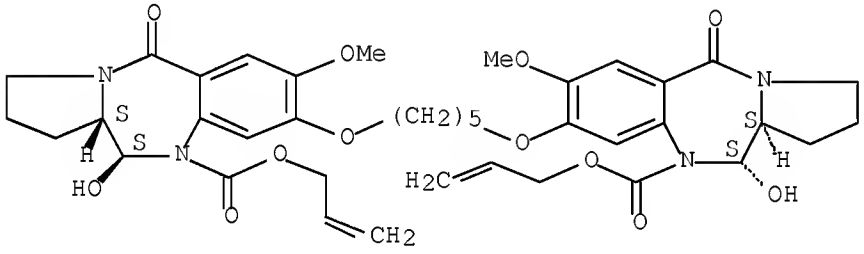
AB Pyrrolobenzodiazepines I [R2, R3 = H, O, OH, CH2, CN, R, OR, O3SR, COR; R = (un)substituted alkyl, heterocyclyl, aryl; R6, R7, R9 = H, R, OH, OR, SH, SR, NH2, NHR, NRR1, NO2, SnMe3, halogen; R1 = (un)substituted alkyl, heterocyclyl, aryl; R8 = H, R, OH, OR, SH, SR, NH2, NHR, NRR1, NO2, SnMe3, halogen, XR4X; R4 = alkylene, heteroalkylene; X = O, S, NH; CO2R10 = protective group; R11 = H, R] were prepared by treating an isocyanatobenzoate with an alc. to form the carbamate, followed by (S)-2-pyrrolidinemethanol, cyclizing, optionally alkylating the resulting OH group. Thus, 2,4,5-O2N(MeO)2C6H2CO2H was amidated with (S)-2-pyrrolidinemethanol, followed by tert-butyldimethylsilyl protection, reduction of the nitro group, and conversion of the amine to isocyanate. The isocyanate was treated with benzyl alc. to give the benzyloxycarboylamine which was desilylated and cyclized with base to give the pyrrolobenzodiazepine II.

IT 848004-77-3P 848004-82-0P 848004-83-1P
848004-84-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of protected pyrrolobenzodiazepines)

RN 848004-77-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

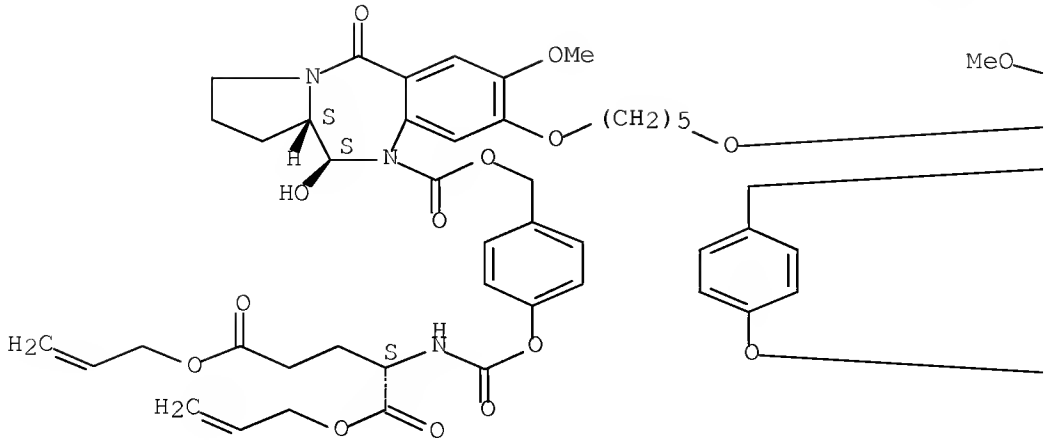


RN 848004-82-0 CAPLUS

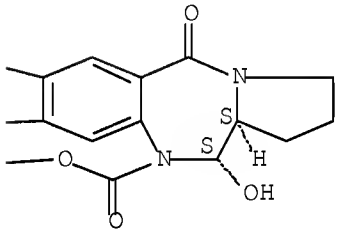
CN L-Glutamic acid, N,N'-[1,5-pentanediylbis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneoxycarbonyl]]bis-, tetra-2-propenyl ester (9CI) (CA INDEX NAME)

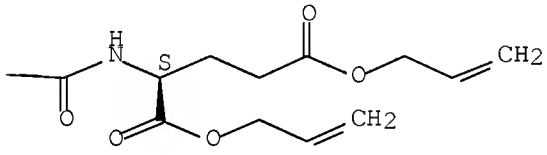
Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 1-B



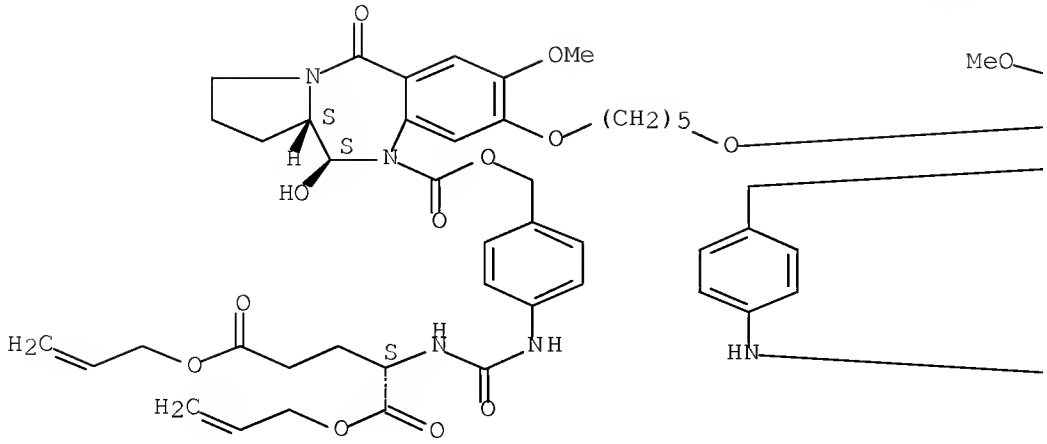


RN 848004-83-1 CAPLUS

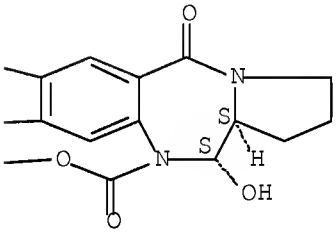
CN L-Glutamic acid, N,N'-[1,5-pentanediylbis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis-, tetra-2-propenyl ester (9CI) (CA INDEX NAME)

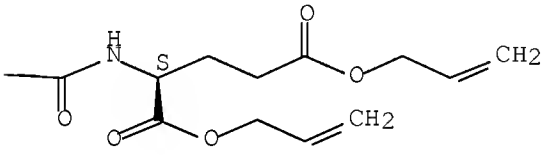
Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 1-B

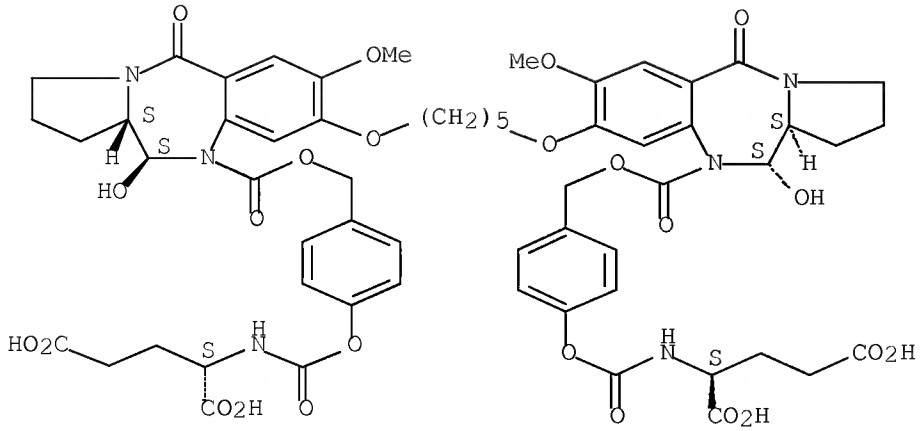




RN 848004-84-2 CAPLUS

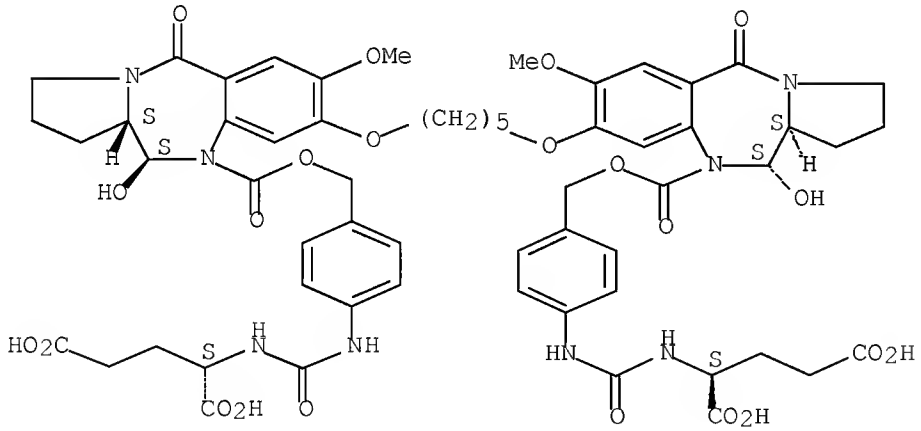
CN L-Glutamic acid, N,N'-[1,5-pentanediylbis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneoxycarbonyl]]bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



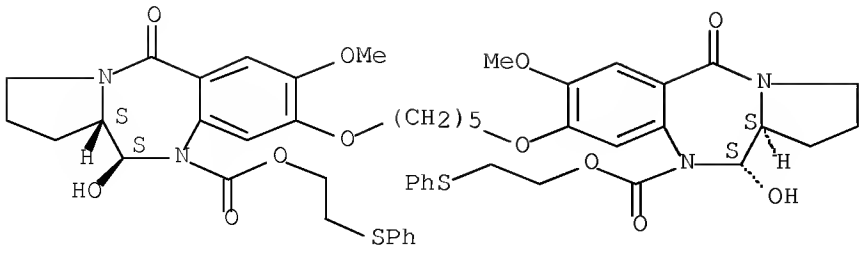
IT 848004-85-3P 848005-10-7P 848005-11-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of protected pyrrolobenzodiazepines)
RN 848004-85-3 CAPLUS
CN L-Glutamic acid, N,N'-[1,5-pentanediylbis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



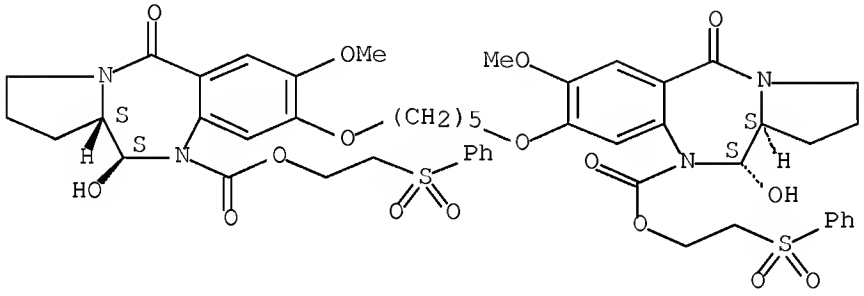
RN 848005-10-7 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[2-(phenylthio)ethyl] ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 848005-11-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[2-(phenylsulfonyl)ethyl] ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:803932 CAPLUS Full-text
DN 141:295775
TI Preparation of non-cross-linking pyrrolo[2,1-c][1,4]benzodiazepines as antitumor agents
IN Kamal, Ahmed; Ramesh, Gujjar; Srinivas, Olepu; Ramulu, Poddutoori
PA Council of Scientific and Industrial Research, India
SO U.S. Pat. Appl. Publ., 13 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004192679	A1	20040930	US 2003-401782	20030331
	US 6884799	B2	20050426		
	CA 2520898	A1	20041014	CA 2003-2520898	20030331
	WO 2004087717	A1	20041014	WO 2003-IB1182	20030331
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	AU 2003215821	A1	20041025	AU 2003-215821	20030331
	EP 1608664	A1	20051228	EP 2003-816509	20030331
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	RU 2314309	C2	20080110	RU 2005-133443	20030331
	IN 2004DN03250	A	20070525	IN 2004-DN3250	20041020
PRAI	US 2003-401782	A	20030331		
	WO 2003-IB1182	W	20030331		

OS CASREACT 141:295775; MARPAT 141:295775
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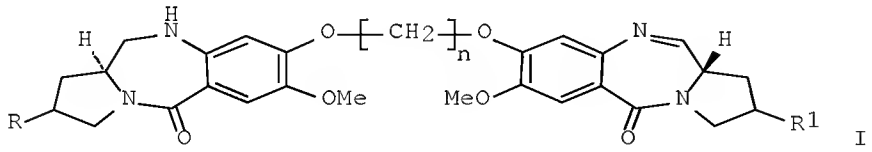


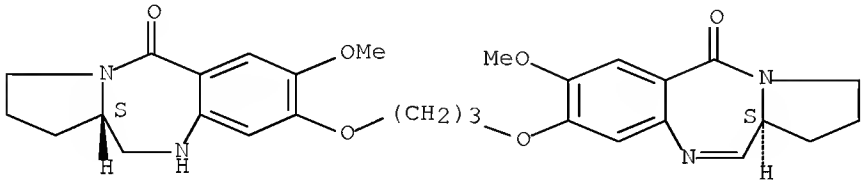
I

AB The present invention relates to novel pyrrolo[2,1-c][1,4]benzodiazepines compds. of formula I [R, R1 = H, OH; n = 3-5], which are useful as potential antitumor agents and a process of preparing these compds. Particularly the present invention provides a process for the preparation of 7-methoxy-8-{n-[7-methoxy-(11aS)-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5-one-8-yloxy]alkyloxy}-(11aS)-1,2,3,11a-tetrahydro- 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one, with varying aliphatic chain length and its 2-hydroxy derivs. Two of the compds. were tested for anticancer activity against several cell lines, which showed that a 3-carbon spacer has slightly higher activity.

IT 763125-64-0P 763125-65-1P 763125-66-2P
763125-67-3P 763125-68-4P 763125-69-5P
763125-71-9P 763125-72-0P 763125-73-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrrolobenzodiazepines as antitumor agents)

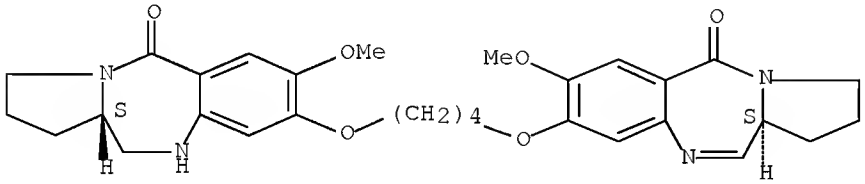
RN 763125-64-0 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



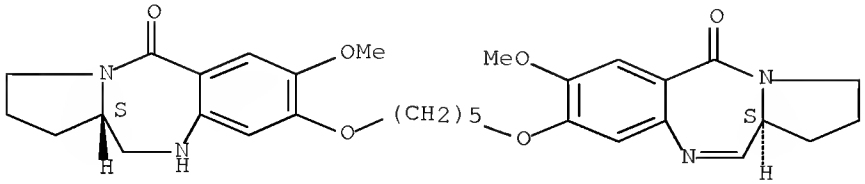
RN 763125-65-1 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 763125-66-2 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (9CI) (CA INDEX NAME)

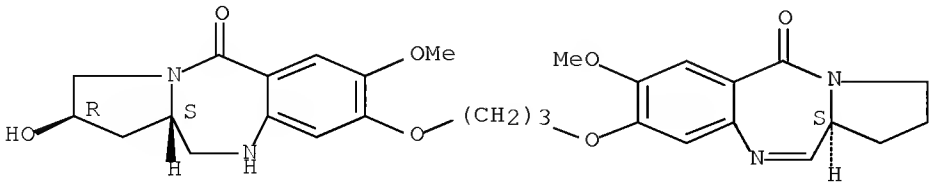
Absolute stereochemistry.



RN 763125-67-3 CAPLUS

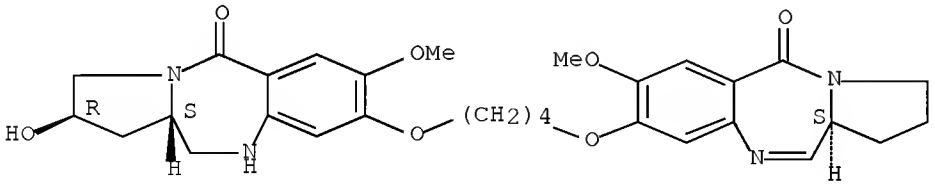
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-2-hydroxy-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



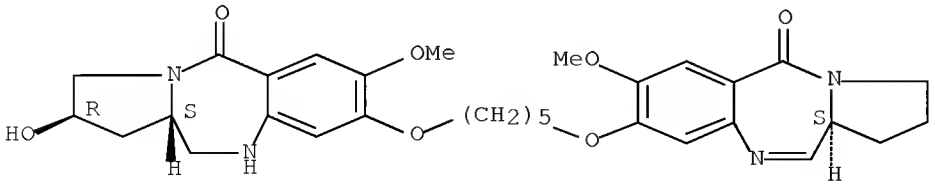
RN 763125-68-4 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-2-hydroxy-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



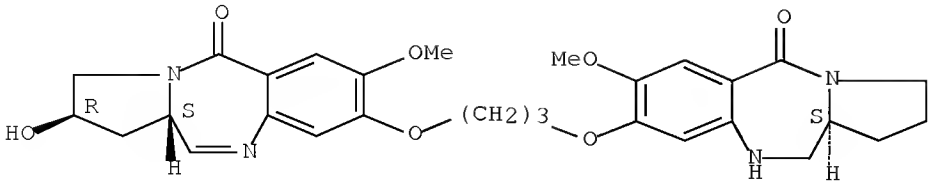
RN 763125-69-5 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-2-hydroxy-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



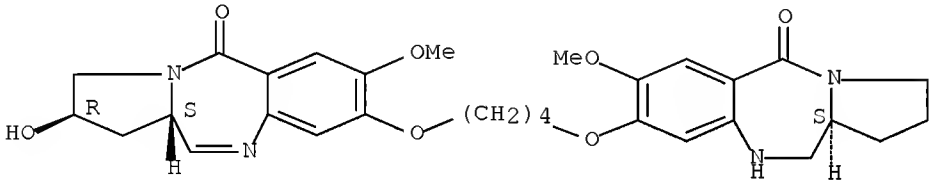
RN 763125-71-9 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8-[3-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-1,2,3,11a-tetrahydro-2-hydroxy-7-methoxy-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



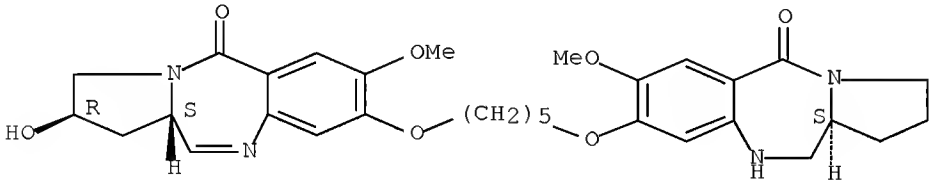
RN 763125-72-0 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8-[4-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-1,2,3,11a-tetrahydro-2-hydroxy-7-methoxy-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



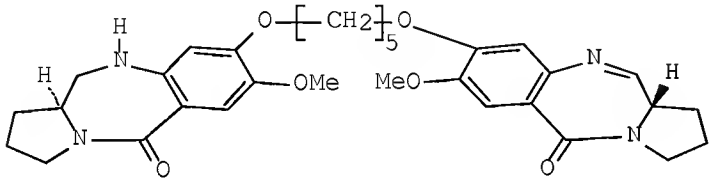
RN 763125-73-1 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8-[[5-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-1,2,3,11a-tetrahydro-2-hydroxy-7-methoxy-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:791713 CAPLUS Full-text
DN 141:342888
TI Design, synthesis, and evaluation of mixed imine-amine pyrrolobenzodiazepine dimers with efficient DNA binding affinity and potent cytotoxicity
AU Kamal, Ahmed; Ramesh, G.; Srinivas, O.; Ramulu, P.; Laxman, N.; Rehana, Tasneem; Deepak, M.; Achary, M. S.; Nagarajaram, H. A.
CS Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500 007, India
SO Bioorganic & Medicinal Chemistry (2004), 12(20), 5427-5436
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Ltd.
DT Journal
LA English
OS CASREACT 141:342888
GI



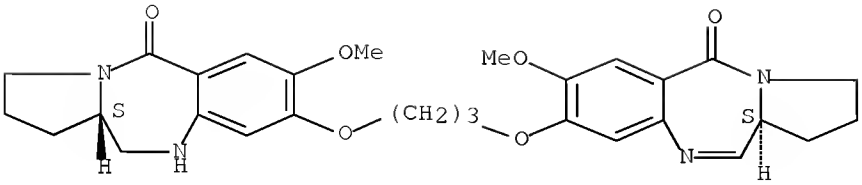
I

AB Synthesis of mixed imine-amine pyrrolobenzodiazepine (PBD) dimers that are comprised of DC-81 and secondary amine (N10) of DC-81 subunits tethered to their C8 positions through alkanedioxy linkers (comprised of three and five carbons) is described. These noncross-linking unsym. mols. exhibit significant DNA minor groove binding ability and one of them I linked through the pentanedioxy chain exhibits efficient DNA binding ability (ΔTm = 11.0 °C) when compared to naturally occurring DC-81 (ΔTm = 0.7 °C). The imine-amine PBD dimers exhibit promising in vitro antitumor activity in a number of human cancer cell lines.

IT 763125-64-0P 763125-66-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pyrrolobenzodiazepine dimers with DNA binding affinity and cytotoxicity)

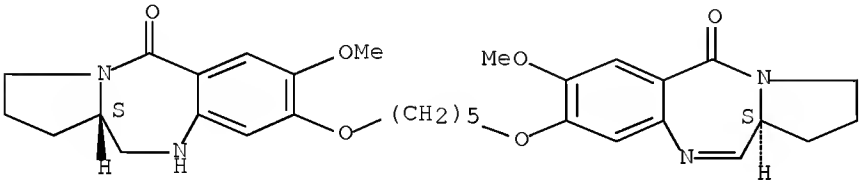
RN 763125-64-0 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



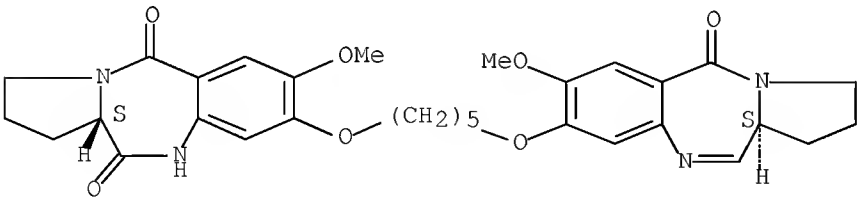
RN 763125-66-2 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,2,3,10,11,11a-hexahydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 343308-45-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pyrrolobenzodiazepine dimers with DNA binding affinity and cytotoxicity)
RN 343308-45-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

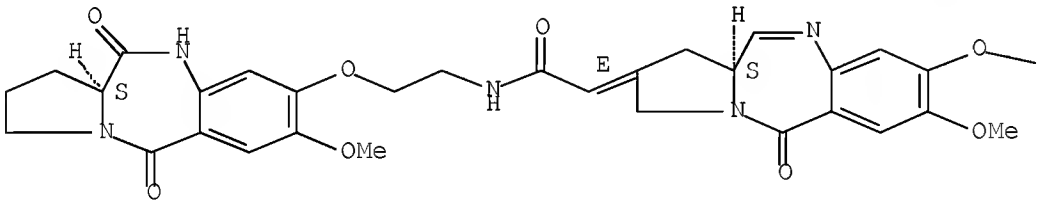


RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

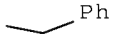
L5 ANSWER 14 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:580808 CAPLUS Full-text
DN 141:277599
TI Synthesis and DNA binding affinity of novel A-C8/C-C2-exo unsaturated alkoxyamido-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers
AU Kamal, Ahmed; Srinivas, O.; Ramulu, P.; Ramesh, G.; Kumar, P. Praveen; Kumar, M. Shiva
CS Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500007, India
SO Bioorganic & Medicinal Chemistry (2004), 12(16), 4337-4350
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Ltd.
DT Journal
LA English
OS CASREACT 141:277599
AB The synthesis of novel A-C8/C-C2-exo unsatd. alkoxyamido-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers is reported and these dimers show significant DNA binding affinity and they also exhibit moderate anticancer activity.
IT 757190-13-9P 757190-14-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(stereoselective preparation, DNA binding affinity and antitumor activity of
unsatd. alkoxyamido-linked pyrrolobenzodiazepine dimers utilizing chiral starting materials)
RN 757190-13-9 CAPLUS
CN Acetamide, 2-[(11aS)-5,11a-dihydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-N-[2-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]ethyl]-, (2E)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

PAGE 1-A



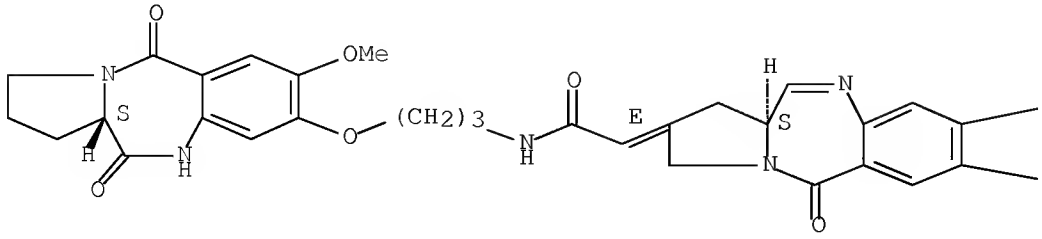
PAGE 1-B



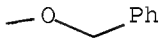
RN 757190-14-0 CAPLUS
CN Acetamide, 2-[(11aS)-5,11a-dihydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-N-[3-[[(11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propyl]-, (2E)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as described by E or Z.

PAGE 1-A



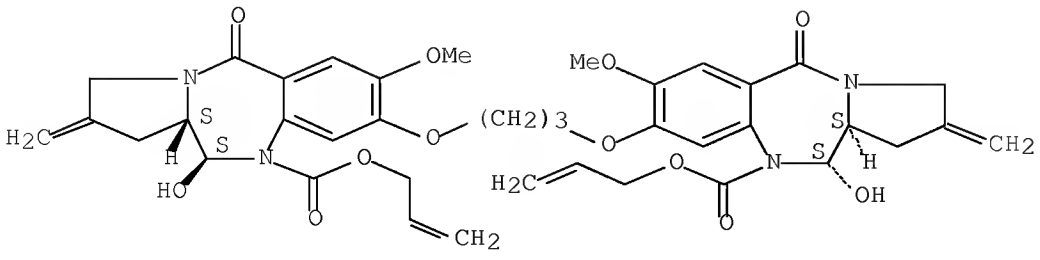
PAGE 1-B



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

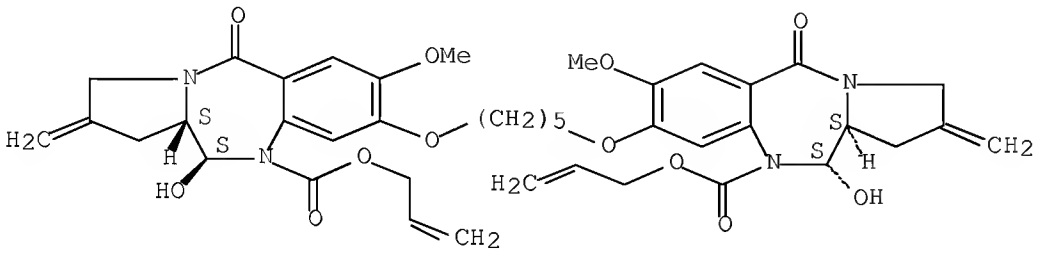
L5 ANSWER 15 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:79123 CAPLUS Full-text
DN 140:280775
TI Linker Length Modulates DNA Cross-Linking Reactivity and Cytotoxic Potency of C8/C8' Ether-Linked C2-exo-Unsaturated Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Dimers
AU Gregson, Stephen J.; Howard, Philip W.; Gullick, Darren R.; Hamaguchi, Anzu; Corcoran, Kathryn E.; Brooks, Natalie A.; Hartley, John A.; Jenkins, Terence C.; Patel, Sejal; Guille, Matthew J.; Thurston, David E.
CS Cancer Research UK Gene Targeted Drug Design Research Group, The School of Pharmacy, University of London, London, WC1N 1AX, UK
SO Journal of Medicinal Chemistry (2004), 47(5), 1161-1174
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 140:280775
AB A C2/C2'-exo-unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimer (DRG-16) with a C8-O(CH2)nO-C8' diether linkage (n = 5) has been synthesized that shows markedly superior in vitro cytotoxic potency (e.g., >3400-fold in IGROV1 ovarian cells) and interstrand DNA crosslinking reactivity (>10-fold) compared to the shorter homolog (SJG-136; n = 3). In contrast, for the C-ring unsubstituted series, the corresponding n = 5 dimer is generally less cytotoxic and has a lower interstrand crosslinking reactivity compared to its shorter n = 3 homolog. Dimer DRG-16 cross-links DNA with >10-fold efficiency compared to 4a, and also inhibits the activity of the restriction endonuclease BamH1 more efficiently. The C2-exo-unsatd. PBD dimers 4a,b are not only more effective than their C-ring saturated counterparts in terms of induced ΔTm shift, but they also exert this effect more rapidly. Mol. modeling shows a rank order of DRG-16 (n = 5) > SJG-136 (n = 3) in terms of binding energy toward duplexes containing embedded target 5'-GAT1-2C cross-link sequences, reflecting the superior fit of the C2-exo-unsatd. rather than saturated C-rings of the PBD dimers. A novel synthesis of core synthetic building blocks for PBD dimers via stepwise Mitsunobu reaction and nitration with Cu(NO3)2 is also reported.
IT 232931-64-5P 260418-31-3P
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(linker length modulates DNA crosslinking reactivity and cytotoxic potency of C8/C8' ether-linked C2-exo-unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimers)
RN 232931-64-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 260418-31-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

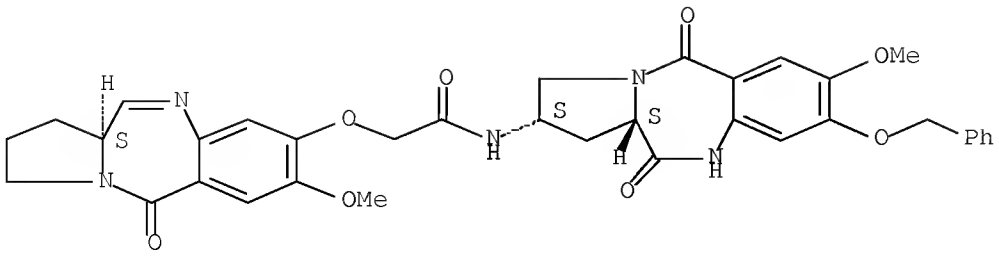
Absolute stereochemistry.



RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:841816 CAPLUS Full-text
DN 140:94019
TI Synthesis and DNA-binding affinity of A-C8/C-C2 alkoxyamido-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers
AU Kamal, Ahmed; Ramulu, P.; Srinivas, O.; Ramesh, G.
CS Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500007, India
SO Bioorganic & Medicinal Chemistry Letters (2003), 13(22), 3955-3958
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science B.V.
DT Journal
LA English
OS CASREACT 140:94019
AB The synthesis of new A-C8/C-C2 alkoxyamido-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers have been described in this report. These dimers exhibit significant DNA-binding ability with moderate anticancer activity. Compds. thus prepared included [[(11aS)-2,3,5,11a-tetrahydro-7- methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)- 2,3,5,11a-tetrahydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]acetamide, 4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]butanamide, 5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]pentanamide. Corresponding dioxo compds., i.e., [[(11aS)-2,3,5,11a-Tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]acetamide and homologs, were also prepared and tested.
IT 642479-12-7P, [[(11aS)-2,3,5,11a-Tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]acetamide 642479-14-9P, 4-[[(11aS)-2,3,5,11a-Tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]butanamide 642479-15-0P, 5-[[(11aS)-2,3,5,11a-Tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]-N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]pentanamide
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and DNA-binding affinity of alkoxyamido-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers)
RN 642479-12-7 CAPLUS
CN Acetamide, N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-2-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (CA INDEX NAME)

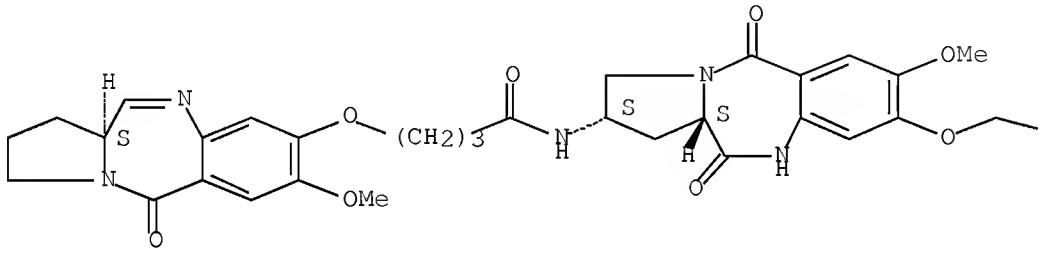
Absolute stereochemistry.



RN 642479-14-9 CAPLUS
CN Butanamide, N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

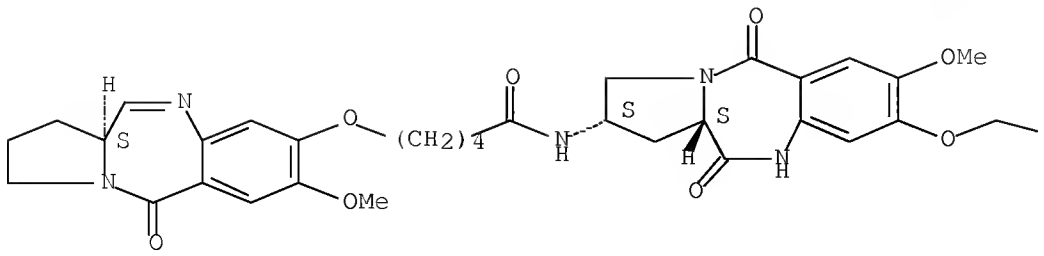


PAGE 1-B

RN 642479-15-0 CAPLUS
CN Pentanamide, N-[(2S,11aS)-2,3,5,10,11,11a-hexahydro-7-methoxy-5,11-dioxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]-5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

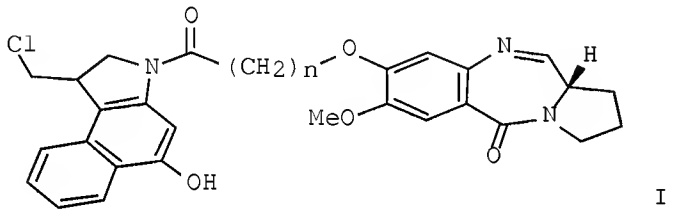


PAGE 1-B

Ph

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:323970 CAPLUS Full-text
DN 139:69239
TI Unsymmetrical DNA Cross-Linking Agents: Combination of the CBI and PBD Pharmacophores
AU Tercel, Moana; Stribbling, Stephen M.; Sheppard, Hilary; Siim, Bronwyn G.; Wu, Kent; Pullen, Susan M.; Botting, K. Jane; Wilson, William R.; Denny, William A.
CS Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, University of Auckland, Auckland, 92019, N. Z.
SO Journal of Medicinal Chemistry (2003), 46(11), 2132-2151
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 139:69239
GI



I

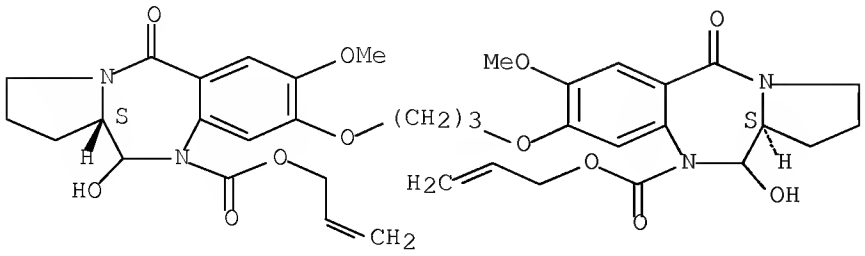
AB A set of chiral amides I (n = 1 - 5), each combining the seco-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one (seco-CBI) and pyrrolo[2,1-c][1,4]benzodiazepine (PBD) pharmacophores, was designed and prepared I were anticipated to cross-link between N3 of adenine and N2 of guanine in the minor groove of DNA. The compds., which differ in the chain length separating the two alkylation subunits, and the configuration of the CBI portion, showed great variation in cellular toxicity (over 4 orders of magnitude in a cell line panel) with the most potent example exhibiting IC50s in the pM range. Cytotoxicity correlated with the ability of I to cross-link naked DNA. Crosslinking was also observed in living cells, at much lower concns. than for a related sym. PBD dimer. A thermal cleavage assay was used to assess sequence selectivity, demonstrating that the CBI portion controlled the alkylation sites, while the PBD substituent increased the overall efficiency of alkylation. Several compds. were tested for in vivo activity using a tumor growth delay assay against WiDr human colon carcinoma xenografts, with (S,S)-I (n = 5) (the most cytotoxic and most efficient cross-linker) showing a statistically significant increase in survival time following a single iv dose.

IT 550356-53-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of chiral (dihydrobenzindolyl)oxoalkoxy pyrrolodiazepinones as unsym. DNA crosslinking and antitumor agents)

RN 550356-53-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-

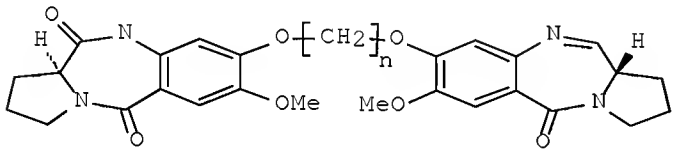
methoxy-5-oxo-, di-2-propenyl ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:702235 CAPLUS Full-text
DN 138:4582
TI Design, Synthesis, and Evaluation of New Noncross-Linking Pyrrolobenzodiazepine Dimers with Efficient DNA Binding Ability and Potent Antitumor Activity
AU Kamal, Ahmed; Ramesh, G.; Laxman, N.; Ramulu, P.; Srinivas, O.; Neelima, K.; Kondapi, Anand K.; Sreenu, V. B.; Nagarajaram, H. A.
CS Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500 007, India
SO Journal of Medicinal Chemistry (2002), 45(21), 4679-4688
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 138:4582
GI



I

AB Pseudodimeric pyrrolobenzodiazepines I (n = 3-5,8) possessing both imine and amide moieties and oxyalkyloxy linkers are prepared and evaluated as DNA-binding compds. for use as potential anticancer agents. I (n = 5) binds to calf thymus DNA and increases the melting temperature of the DNA by 17°, comparable or greater than the increase in DNA melting temperature by other DNA binding agents. The length of the linker affects the binding of I significantly; while I (n = 5) increases the melting temperature of DNA by 17°, I (n = 8) increases the melting temperature of DNA by only 0.7°. I (n = 3-5) are tested for their cytotoxicities against a variety of human cancer cell lines; I (n = 3-5) kill 50% of the cancer cells at concentration of 10-100 μM. The binding of I (n = 3-5, 8) to a 15 base pair sequence of DNA is simulated; the binding affinities calculated correspond well to the exptl. binding affinities, with I (n = 5) stabilizing DNA helixes more effectively than I (n = 3,4,8). The energy of interaction in all of the complexes studied is correlated to the change in DNA melting temperature Both noncovalent and covalent interactions are important in understanding the affinities of I for DNA and their antitumor activities.
IT 477207-67-3 477207-69-5 477207-98-0
477208-74-5
RL: PRP (Properties)
(calculated energies of interaction of oxyalkyloxy-linked pseudodimers of pyrrolo[2,1-c][1,4]benzodiazepines with 15 base pair DNA sequences)
RN 477207-67-3 CAPLUS
CN DNA, d(G-G-G-G-C-G-A-G-A-G-A-G-G-G-G), compd. with (11aS)-2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione (1:1) (9CI) (CA INDEX NAME)

CM 1

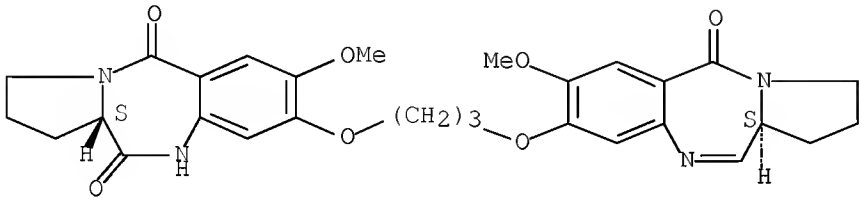
CRN 477207-55-9
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 343308-43-0
CMF C29 H32 N4 O7

Absolute stereochemistry. Rotation (+).



RN 477207-69-5 CAPLUS
CN DNA, d(G-G-G-G-C-G-A-G-A-G-A-G-G-G-G), compd. with (11aS)-2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione (1:1) (9CI) (CA INDEX NAME)

CM 1

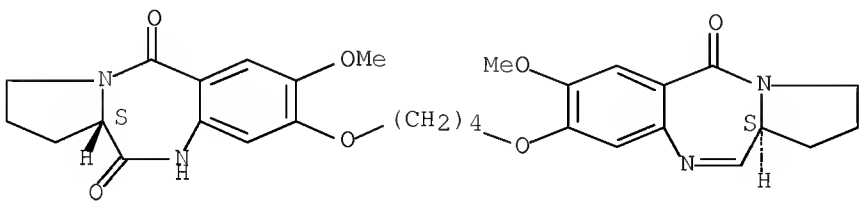
CRN 477207-55-9
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 343308-44-1
CMF C30 H34 N4 O7

Absolute stereochemistry. Rotation (+).



RN 477207-98-0 CAPLUS
CN DNA, d(G-G-G-G-C-G-A-G-A-G-A-G-G-G-G), compd. with (11aS)-2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-

c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-1H-pyrrolo[2,1-
c][1,4]benzodiazepine-5,11(10H,11aH)-dione (1:1) (9CI) (CA INDEX NAME)

CM 1

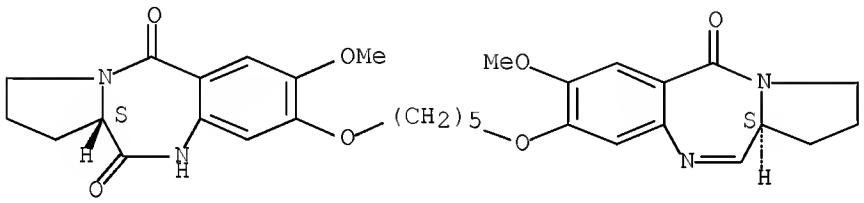
CRN 477207-55-9
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 343308-45-2
CMF C31 H36 N4 O7

Absolute stereochemistry. Rotation (+).



RN 477208-74-5 CAPLUS
CN DNA, d(G-G-G-G-C-G-A-G-A-G-A-G-G-G-G), compd. with (11aS)-2,3-dihydro-7-methoxy-8-[[8-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]octyl]oxy]-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione (1:1) (9CI) (CA INDEX NAME)

CM 1

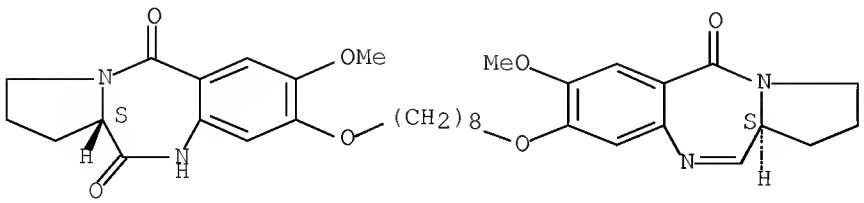
CRN 477207-55-9
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 476015-23-3
CMF C34 H42 N4 O7

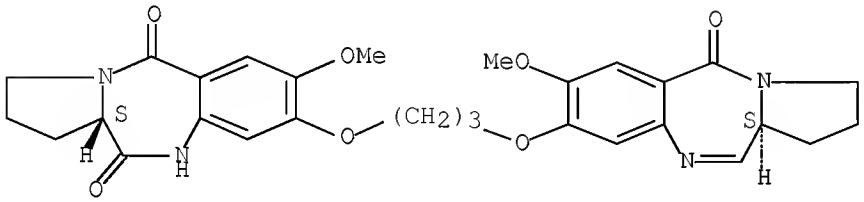
Absolute stereochemistry. Rotation (+).



IT 343308-43-0D, calf thymus DNA-bound 343308-44-1D, calf thymus DNA-bound 343308-45-2D, calf thymus DNA-bound 476015-23-3D, calf thymus DNA-bound
RL: PRP (Properties)
(increase of DNA melting temperature upon binding of oxyalkyloxy-linked pseudodimers of pyrrolo[2,1-c][1,4]benzodiazepines to calf thymus DNA)

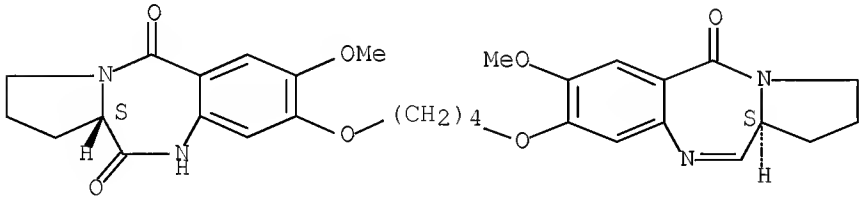
RN 343308-43-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



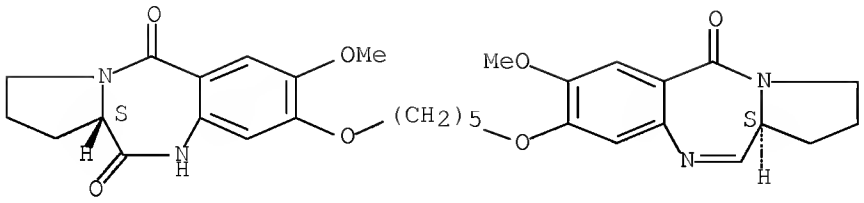
RN 343308-44-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



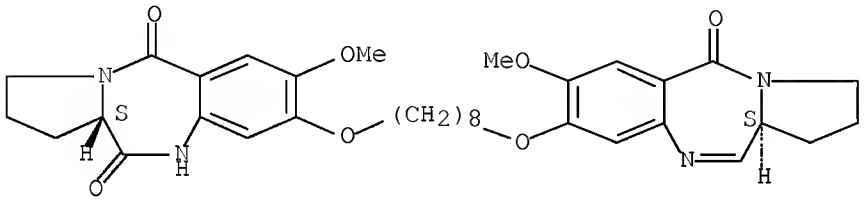
RN 343308-45-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 476015-23-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[8-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]octyl]oxy]-, (11aS)- (CA INDEX NAME)

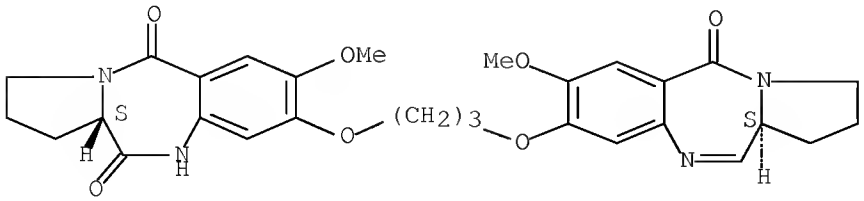
Absolute stereochemistry. Rotation (+).



IT 343308-43-0P 343308-44-1P 343308-45-2P
476015-23-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of oxyalkyloxy-linked pseudodimers of pyrrolo[2,1-c][1,4]benzodiazepines as DNA binding and antitumor agents)

RN 343308-43-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX NAME)

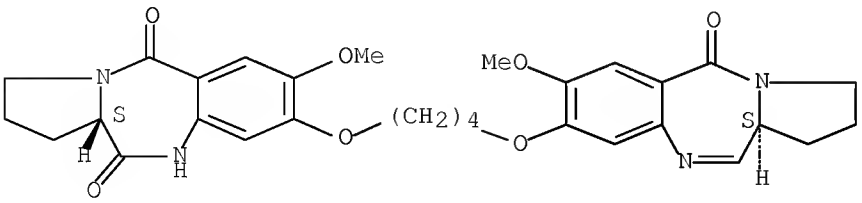
Absolute stereochemistry. Rotation (+).



RN 343308-44-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-

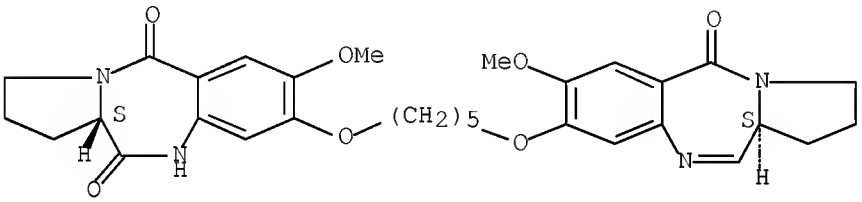
1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



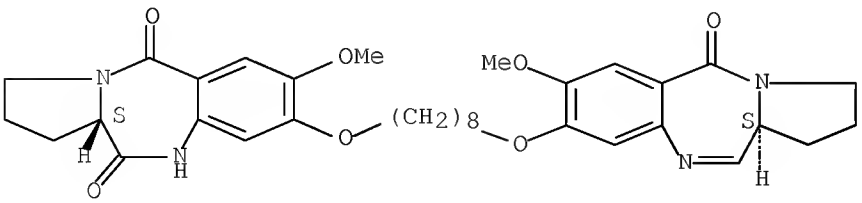
RN 343308-45-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 476015-23-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[8-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]octyl]oxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

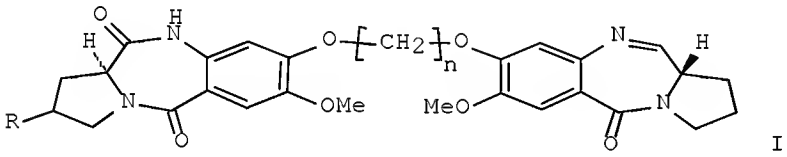


RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:237375 CAPLUS Full-text
DN 136:263030
TI Preparation of pyrrolobenzodiazepines as antitumor agents
IN Kamal, Ahmed; Nallan, Chakravarthy Laxman; Gujjar, Ramesh; Poddutoori, Ramulu; Olepu, Srinivas
PA Council of Scientific and Industrial Research, India
SO U.S., 12 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6362331	B1	20020326	US 2001-822782	20010330
PRAI US 2001-822782		20010330		

OS CASREACT 136:263030; MARPAT 136:263030
GI



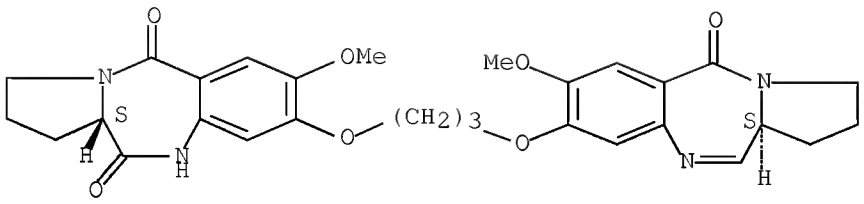
I

AB The present invention provides a process for the preparation of a novel pyrrolo[2,1-c][1,4]benzodiazepine of formula I [R = H, OH, OAc; n = 3-5], by reacting (2S)-N-[4-hydroxy-5-methoxy-2-nitrobenzyl]-pyrrolidine-2-carboxaldehyde di-Et thioacetal with a dibromoalkane, isolating (2S)-N-[4-(3-bromoalkoxy)-5-methoxy-2-nitrobenzoyl]pyrrolidine-2- carboxaldehyde di-Et thioacetal so formed and reacting the isolate with a dilactam, isolating 8-{[(2S)-N-5-methoxy-2-nitrobenzoyl]pyrrolidin-2- carbaldehyde diethylthioacetal}-alkoxy-7-methoxy-2,3,5,10,11,11a-hydro-1H- pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione, reducing the above nitro compound, isolating the 8-[[(2S)-N-5-methoxy-2-aminobenzoyl]pyrrolidin-2- carbaldehyde diethylthioacetal]-alkoxy-7-methoxy-2,3,5,10,11,11a-hydro-1H- pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione, reacting the amino compound above with a deprotecting agent to obtain the pyrrolo[2,1- c][1,4]benzodiazepines. The pyrrolo[2,1-c][1,4]benzodiazepines are useful as antitumor agents. Thus, II (R = H, n = 5) was prepared as described above and showed significant DNA binding affinity and anticancer activity against three human cell lines.

IT 343308-43-0P 343308-44-1P 343308-45-2P
405108-10-3P 405108-11-4P 405108-12-5P
405108-13-6P 405108-14-7P 405108-15-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrrolobenzodiazepines as antitumor agents)

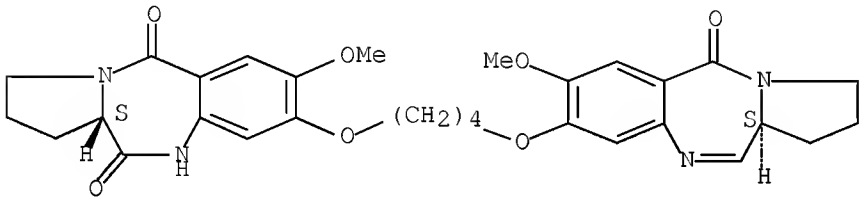
RN 343308-43-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



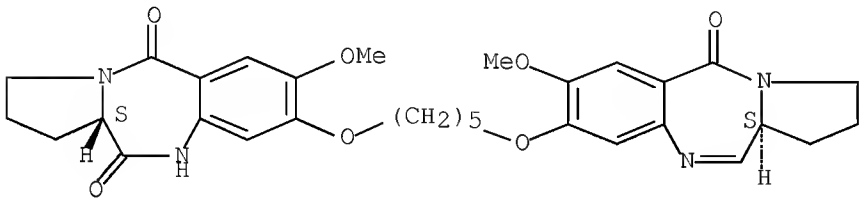
RN 343308-44-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



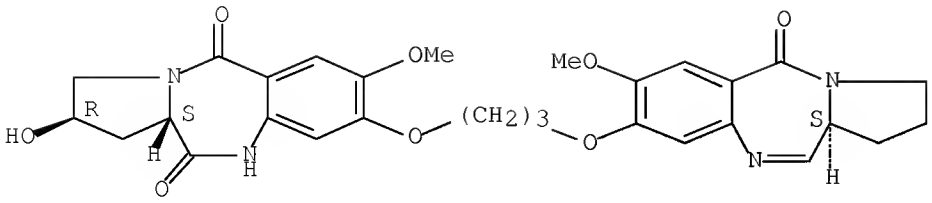
RN 343308-45-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



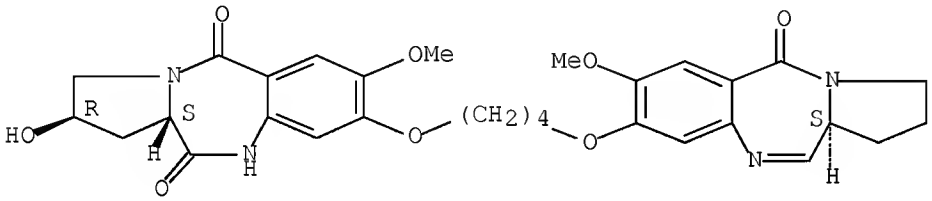
RN 405108-10-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-2-hydroxy-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



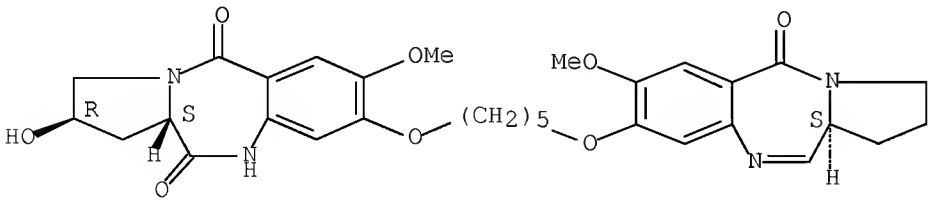
RN 405108-11-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-2-hydroxy-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



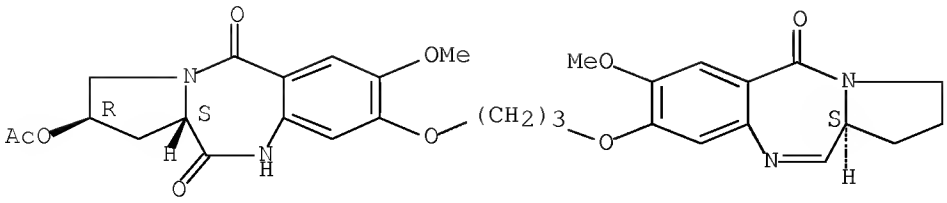
RN 405108-12-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-2-hydroxy-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



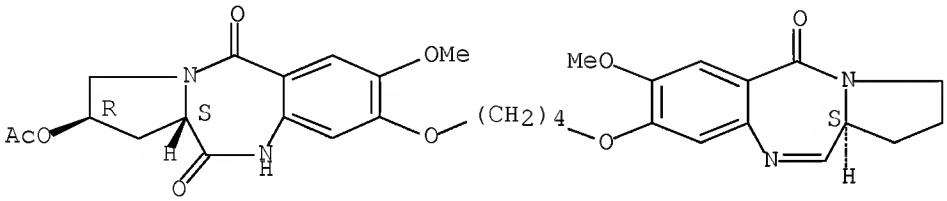
RN 405108-13-6 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



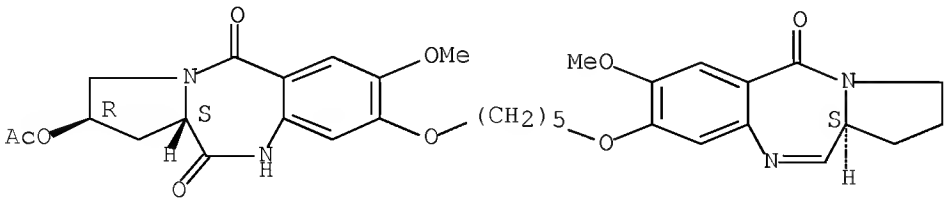
RN 405108-14-7 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.



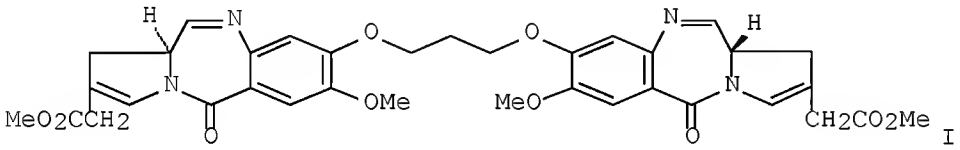
RN 405108-15-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (2R,11aS)- (CA INDEX NAME)

Absolute stereochemistry.

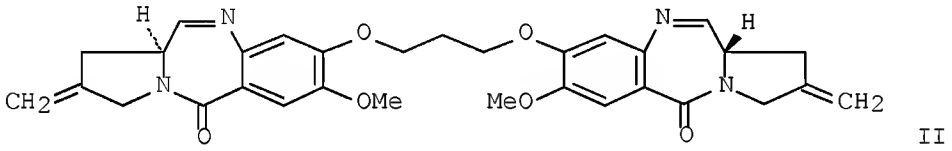


RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:746612 CAPLUS Full-text
DN 136:200170
TI Synthesis of the first example of a C2-C3/C2'-C3'-endo unsaturated pyrrolo[2,1-c][1,4]benzodiazepine dimer
AU Gregson, S. J.; Howard, P. W.; Corcoran, K. E.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E.
CS Cancer Research Laboratories, CRC Gene Targeted Drug Design Research Group, University of Nottingham, School of Pharmaceutical Sciences, Nottingham, NG7 2RD, UK
SO Bioorganic & Medicinal Chemistry Letters (2001), 11(21), 2859-2862
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 136:200170
GI



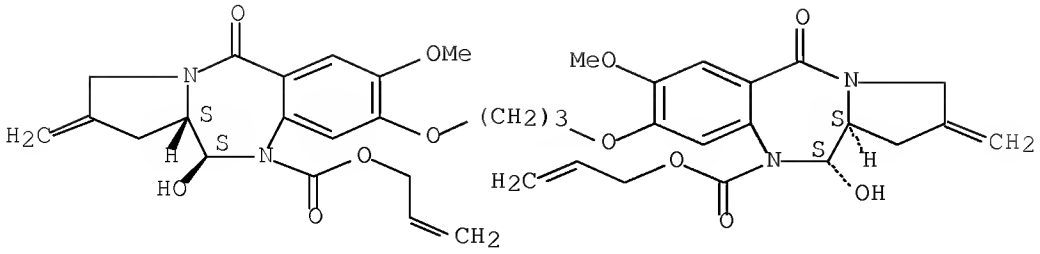
I



II

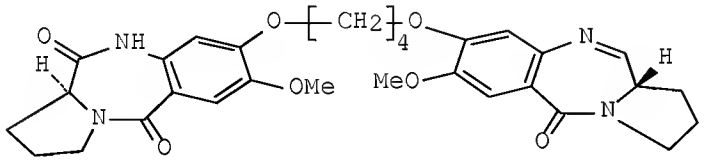
AB We report the first example of a C2-C3/C2'-C3'-endo unsatd. pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimer (I) synthesized through a new and efficient route, thus establishing that C2-C3-endo unsatn. enhances both cytotoxicity and DNA-binding affinity in A-ring-linked PBD dimers but to a lesser extent than C2/C2'-exo-unsatn. This new route has allowed the preparation of multigram quantities of the related clin. candidate II and should lead to more structurally diverse PBD dimer analogs.
IT 232931-64-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of first example of C2-C3/C2'-C3'-endo unsatd. pyrrolo[2,1-c][1,4]benzodiazepine dimer)
RN 232931-64-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:139435 CAPLUS Full-text
DN 135:13847
TI Synthesis of novel non-cross-linking pyrrolobenzodiazepines with remarkable DNA binding affinity and potent antitumour activity
AU Kamal, Ahmed; Laxman, N.; Ramesh, G.; Neelima, K.; Kondapi, Anand K.
CS Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, 500 007, India
SO Chemical Communications (Cambridge, United Kingdom) (2001), (5), 437-438
CODEN: CHCOFS; ISSN: 1359-7345
PB Royal Society of Chemistry
DT Journal
LA English
OS CASREACT 135:13847
GI



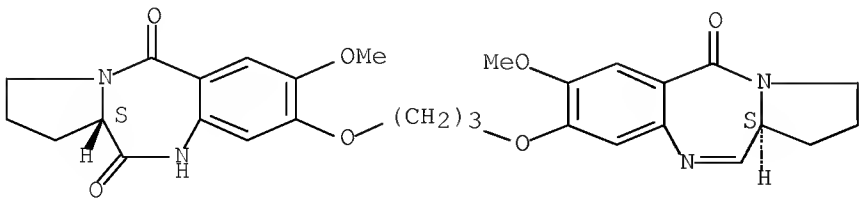
I

AB Mixed imine-amide pyrrolobenzodiazepine dimers have been prepared which exhibit potent antitumor activity and have significant DNA binding affinity; one of them, I, has been shown to cause a remarkable rise in the melting temperature of calf thymus DNA.

IT 343308-43-0P 343308-44-1P 343308-45-2P
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(pyrrolobenzodiazepines with DNA binding affinity and antitumor activity)

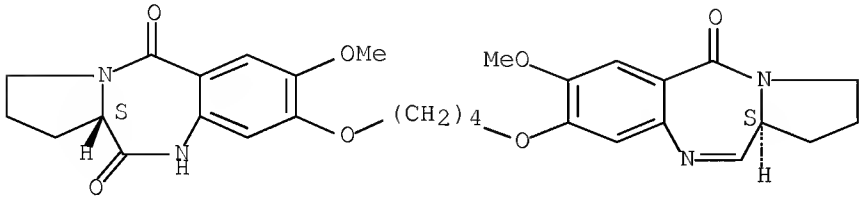
RN 343308-43-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



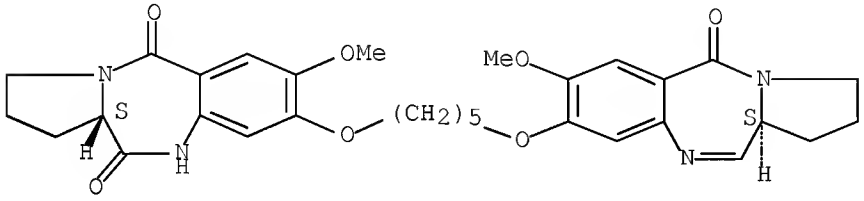
RN 343308-44-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 343308-45-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (CA INDEX NAME)

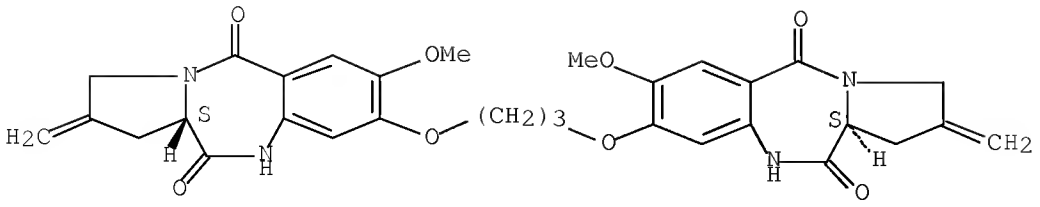
Absolute stereochemistry. Rotation (+).



RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:68712 CAPLUS Full-text
DN 134:260871
TI Design, synthesis, and evaluation of a novel pyrrolobenzodiazepine DNA-interactive agent with highly efficient cross-linking ability and potent cytotoxicity
AU Gregson, Stephen J.; Howard, Philip W.; Hartley, John A.; Brooks, Natalie A.; Adams, Lesley J.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston, David E.
CS CRC Gene Targeted Drug Design Research Group, Cancer Research Laboratories University of Nottingham, Nottingham, NG7 2RD, UK
SO Journal of Medicinal Chemistry (2001), 44(5), 737-748
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 134:260871
AB A novel sequence-selective pyrrolobenzodiazepine (PBD) dimer 5 (SJG-136) has been developed that comprises two C2-exo-methylene-substituted DC-81 (3) subunits tethered through their C8 positions via an inert propanedioxy linker. This sym. mol. is a highly efficient minor groove interstrand DNA crosslinking agent (XL50 = 0.045 μM) that is 440-fold more potent than melphalan. Thermal denaturation studies show that, after 18 h incubation with calf thymus DNA at a 5:1 DNA/ligand ratio, it increases the Tm value by 33.6°, the highest value so far recorded in this assay. The analogous dimer 4 (DSB-120) that lacks substitution/unsatn. at the C2 position elevates melting by only 15.1° under the same conditions, illustrating the effect of introducing C2-exo-unsatn. which serves to flatten the C-rings and achieve a superior isohelical fit within the DNA minor groove. This behavior is supported by mol. modeling studies which indicate that (i) the PBD units are covalently bonded to guanines on opposite strands to form a cross-link, (ii) 5 has a greater binding energy compared to 4, and (iii) 4 and 5 have equivalent binding sites that span six base pairs. Dimer 5 is significantly more cytotoxic than 4 in a number of human ovarian cancer cell lines (e.g., IC50 values of 0.0225 nM vs. 7.2 nM, resp., in A2780 cells). Furthermore, it retains full potency in the cisplatin-resistant cell line A2780cisR (0.024 nM), whereas 4 loses activity (0.21 μM) with a resistance factor of 29.2. This may be due to a lower level of inactivation of 5 by intracellular thiol-containing mols. A dilactam analog, tetralactam of 5 that lacks the electrophilic N10-C11/N10'-C11' imine moieties has also been synthesized and evaluated. Although unable to interact covalently with DNA, tetralactam still stabilizes the helix (ΔTm = 0.78°) and has significant cytotoxicity in some cell lines (i.e., IC50 = 0.57 μM in CH1 cells), presumably exerting its effect through noncovalent interaction with DNA.
IT 232931-67-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design, synthesis, and evaluation of a novel pyrrolobenzodiazepine DNA-interactive agent with highly efficient crosslinking ability and potent cytotoxicity)
RN 232931-67-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

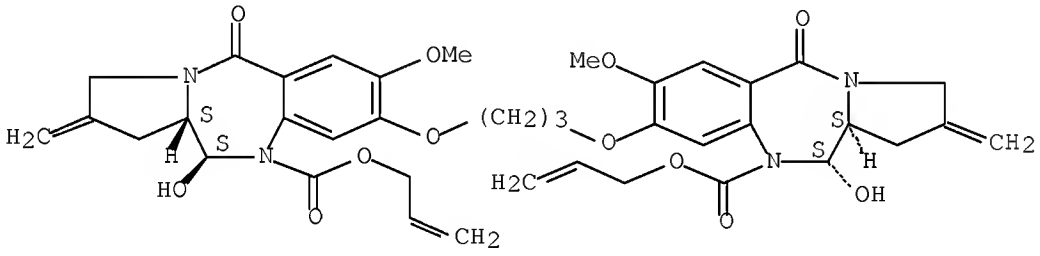


IT 232931-64-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design, synthesis, and evaluation of a novel pyrrolobenzodiazepine DNA-interactive agent with highly efficient crosslinking ability and potent cytotoxicity)

RN 232931-64-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

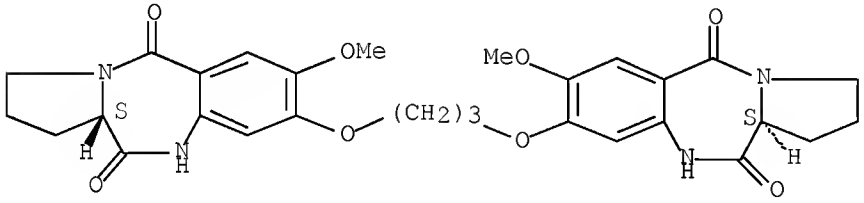
Absolute stereochemistry.



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

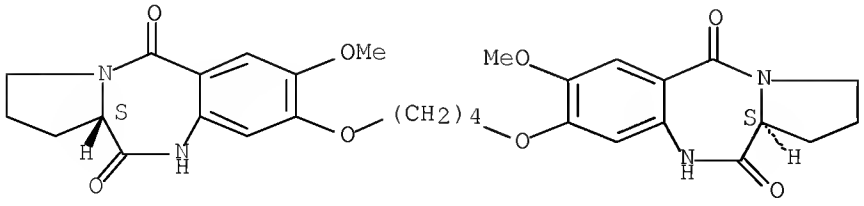
L5 ANSWER 23 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:719703 CAPLUS Full-text
DN 134:56501
TI Synthesis of pyrrolo[2,1-c][1,4]benzodiazepines via reductive cyclization of ω-azido carbonyl compounds by TMSI: an efficient preparation of antibiotic DC-81 and its dimers
AU Kamal, A.; Laxman, E.; Laxman, N.; Venugopal Rao, N.
CS Division of Organic Chemistry-I, Indian Institute of Chemical Technology, Hyderabad, 500 007, India
SO Bioorganic & Medicinal Chemistry Letters (2000), 10(20), 2311-2313
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 134:56501
AB ω-Azido carbonyl compds. on reaction with trimethylsilyl iodide (in situ prepared from TMSCl/NaI) led to the formation of diazepine imines in good yields under mild conditions. This methodol. has been applied to the parent unsubstituted pyrrolobenzodiazepine, the natural product DC-81 and its dimers.
IT 313644-35-8P 313644-44-9P 313644-45-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(efficient synthesis of antibiotic DC-81 and its dimers via reductive cyclization of ω-azido carbonyl compds. by TMSI)
RN 313644-35-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



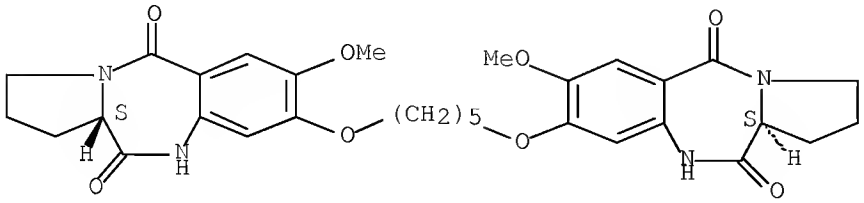
RN 313644-44-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,4-butanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 313644-45-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,5-pentanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

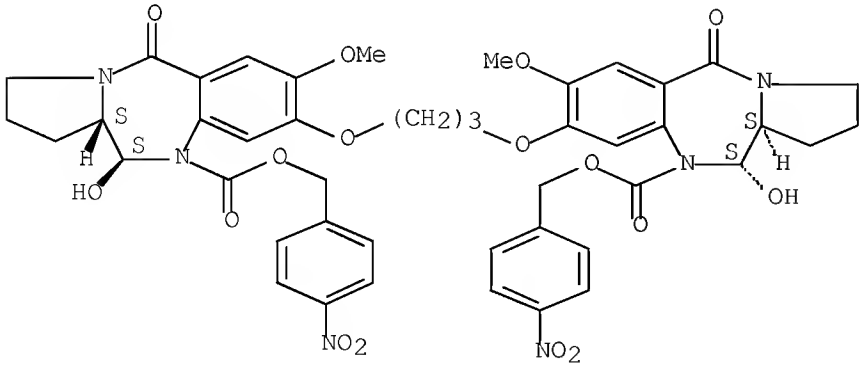
Absolute stereochemistry.



RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 24 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:619247 CAPLUS Full-text
DN 133:362758
TI Design and synthesis of novel pyrrolobenzodiazepine (PBD) prodrugs for ADEPT and GDEPT
AU Sagnou, M. J.; Howard, P. W.; Gregson, S. J.; Eno-Amooquaye, E.; Burke, P. J.; Thurston, D. E.
CS School of Pharmacy and Biomedical Sciences, CRC Gene Targeting Drug Design Research Group, University of Portsmouth, Hants, PO1 2DT, UK
SO Bioorganic & Medicinal Chemistry Letters (2000), 10(18), 2083-2086
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 133:362758
AB Three N10-(4-nitrobenzyl)carbamate-protected PBD prodrugs were prepared and evaluated for potential use in nitro reductase-based ADEPT (antibody-directed enzyme chemotherapy) and GDEPT (gene-directed chemotherapy). For example, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5- oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)- carboxylic acid (4-nitrophenyl)methyl ester was prepared, which is a prodrug precursor to benzyl DC 81. An approx. 100-fold activation was observed for benzyl DC 81.
IT 307925-16-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrrolobenzodiazepine prodrugs for antibody-directed enzyme chemotherapy (ADEPT) and gene-directed enzyme chemotherapy (GEDEPT))
RN 307925-16-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4-nitrophenyl)methyl] ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

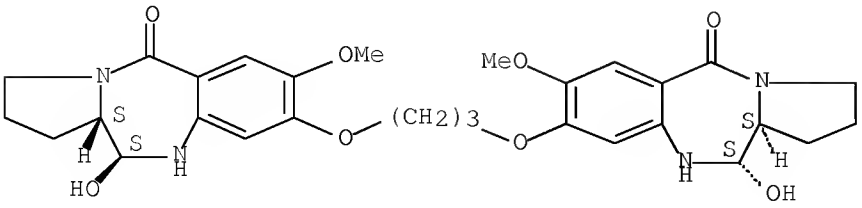
Absolute stereochemistry.



IT 307925-17-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of pyrrolobenzodiazepine prodrugs for antibody-directed enzyme chemotherapy (ADEPT) and gene-directed enzyme chemotherapy (GEDEPT))
RN 307925-17-3 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-11-hydroxy-7-methoxy-,

(11S,11'S,11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 25 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:161284 CAPLUS Full-text
DN 132:207851
TI Preparation of pyrrolobenzodiazepines (PBDs) as antitumor agents
IN Thurston, David Edwin; Howard, Philip Wilson
PA The University of Portsmouth Higher Education Corporation, UK
SO PCT Int. Appl., 258 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000012508	A2	20000309	WO 1999-GB2838	19990827
	WO 2000012508	A3	20000921		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2341471	A1	20000309	CA 1999-2341471	19990827
	AU 9956351	A	20000321	AU 1999-56351	19990827
	AU 757510	B2	20030220		
	EP 1109812	A2	20010627	EP 1999-943066	19990827
	EP 1109812	B1	20050504		
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	EP 1193270	A2	20020403	EP 2001-129700	19990827
	EP 1193270	A3	20020417		
	EP 1193270	B1	20030514		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002525285	T	20020813	JP 2000-571054	19990827
	AT 240334	T	20030515	AT 2001-129700	19990827
	PT 1193270	T	20031031	PT 2001-129700	19990827
	NZ 510493	A	20031128	NZ 1999-510493	19990827
	ES 2199200	T3	20040216	ES 2001-129700	19990827
	EP 1413582	A1	20040428	EP 2003-28817	19990827
	EP 1413582	B1	20060315		
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	AT 294803	T	20050515	AT 1999-943066	19990827
	PT 1109812	T	20050930	PT 1999-943066	19990827
	ES 2244210	T3	20051201	ES 1999-943066	19990827
	AT 320436	T	20060415	AT 2003-28817	19990827
	PT 1413582	T	20060731	PT 2003-28817	19990827
	ES 2260570	T3	20061101	ES 2003-28817	19990827
	US 7049311	B1	20060523	US 2001-763767	20010226
	US 2003120069	A1	20030626	US 2001-21213	20011212
	US 7067511	B2	20060627		
	US 2006148788	A1	20060706	US 2006-367241	20060302
	US 7265105	B2	20070904		
PRAI	GB 1998-18733	A	19980827		
	GB 1999-1929	A	19990128		
	EP 1999-943066	A3	19990827		
	WO 1999-GB2838	W	19990827		
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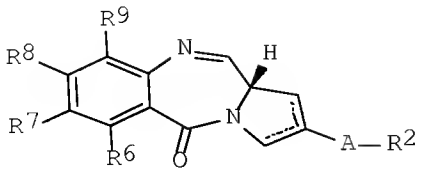
OS MARPAT 132:207851

GI



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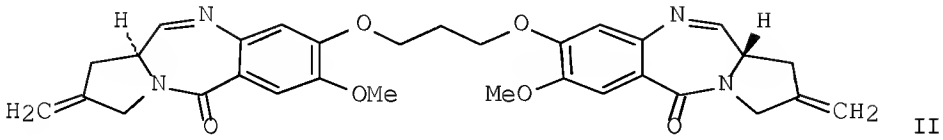


II

AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein A = CH2 or a single bond; R = (un)substituted (ar)alkyl, (ar)alkenyl, or (ar)alkynyl; R2 = R, OH, OR, CO2H, CO2R, COH, COR, SO2R, CN; R6, R7, R8, and R9 = independently H, R, OH, OR, halo, NH2, NHR, NO2, SnMe3; or the compound is a dimer with each monomer being the same or different and being of formula I and the R8 groups of the monomers form a -X-R'-X- bridge, where R' is an alkylene chain which may contain ≥ 1 heteroatoms and/or aromatic rings and/or carbon-carbon double or triple bonds, and each X = independently O, S, or N] were prepared for the treatment of gene-based diseases, e.g. neoplastic diseases and Alzheimer's disease, and also bacterial, parasitic, and viral infections. For example, II was synthesized in a 6-step sequence. 1',3'-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)propane (preparation given) was bisamidated with (2S)-2-(tert-butyldimethylsilyloxymethyl)-4-methylenepyrrolidine (74%). TBAF-mediated cleavage of the silyl protecting groups (94%), followed by reduction of the nitro groups by NH2NH2 in the presence of Raney Ni (63%) and N-acylation with allyl chloroformate (50%), gave the protected diamine. Ring closure was accomplished under Swern oxidation conditions, (COCl)2-DMSO and TEA, (32%). Finally, the imine was formed from the carbinolamine by N-deprotection using Pd(PPh3)4 and elimination of H2O (77%). Both large scale in vitro cytotoxicity cell screens and and in vivo hollow fiber and human tumor xenograft assays were performed on selected compds. of the invention. For instance, II exhibited potent and selective cytotoxicity against the lung cancer cell line NCI-H460, the colon cell line HCC-2998, the CNS cancer cell line SNB-75, and the melanoma cell lines MALME-3M (very potent, 0.08 μM) and UACC-62 (very potent, 0.07 μM). In human xenograft studies against five types of tumors, II demonstrated anticancer activity with mixed toxicity results. In addition, II was shown to be the most potent DNA-stabilizing agent known to date according to a DNA helix melting temperature assay. The IC50 value for II in the A2780 human ovarian carcinoma cell line was only 23 pM, a 320-fold increase in cytotoxicity compared to the known antitumor agent DSB-120 (IC50 = 5.2 nM). Remarkably, II was also almost 9000-fold more potent in the cisplatin-resistant A2780cisR cell line (IC50 = 24 pM) than DSB-120 (IC50 = 0.21 mM), suggesting that II may have potential in the treatment of cisplatin-refractory disease.

IT 232931-64-5P 260418-31-3P 260418-44-8P

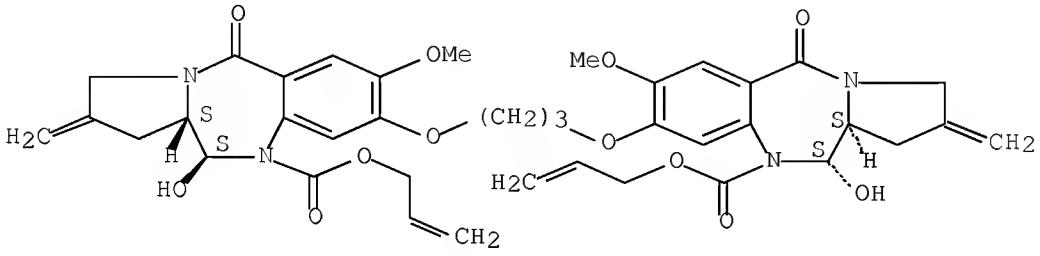
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

RN 232931-64-5 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

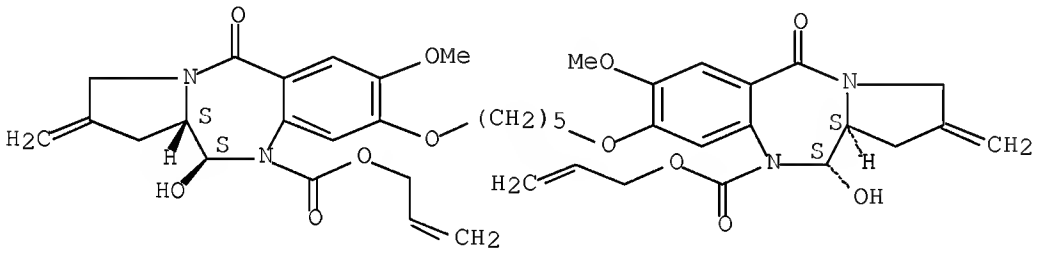
Absolute stereochemistry.



RN 260418-31-3 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,5-pentanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

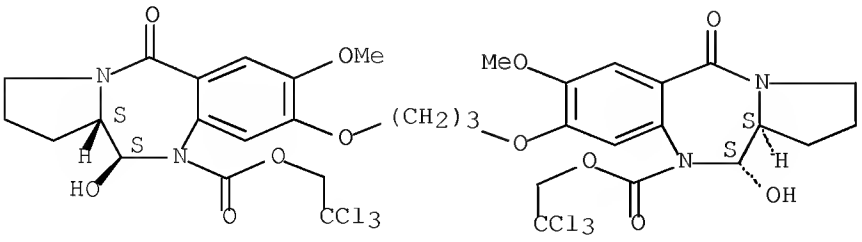
Absolute stereochemistry.



RN 260418-44-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis(2,2,2-trichloroethyl) ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 26 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:161283 CAPLUS Full-text
DN 132:207703
TI Preparation of pyrrolobenzodiazepines (PBDs) as antitumor antibiotics
IN Thurston, David Edwin; Howard, Philip Wilson
PA The University of Portsmouth Higher Education Corporation, UK
SO PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000012507	A2	20000309	WO 1999-GB2837	19990827
	WO 2000012507	A3	20000831		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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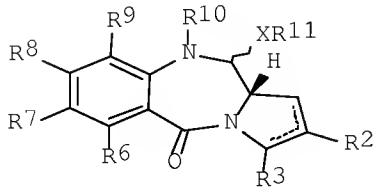
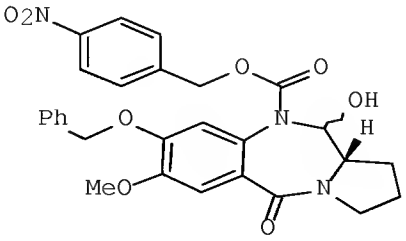
	CA 2341968	A1	20000309	CA 1999-2341968	19990827
	AU 9955261	A1	20000321	AU 1999-55261	19990827
	AU 758398	B2	20030320		
	EP 1109811	A2	20010627	EP 1999-941766	19990827
	EP 1109811	B1	20030806		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002525284	T	20020813	JP 2000-571053	19990827
	AT 246687	T	20030815	AT 1999-941766	19990827
	NZ 510492	A	20030829	NZ 1999-510492	19990827
	PT 1109811	T	20031231	PT 1999-941766	19990827
	ES 2205872	T3	20040501	ES 1999-941766	19990827
	US 6562806	B1	20030513	US 2001-763814	20010226
	US 2003195196	A1	20031016	US 2003-379049	20030304
PRAI	GB 1998-18731	A	19980827		
	WO 1999-GB2837	W	19990827		
	US 2001-763814	A1	20010226		

OS MARPAT 132:207703
GI



I



II

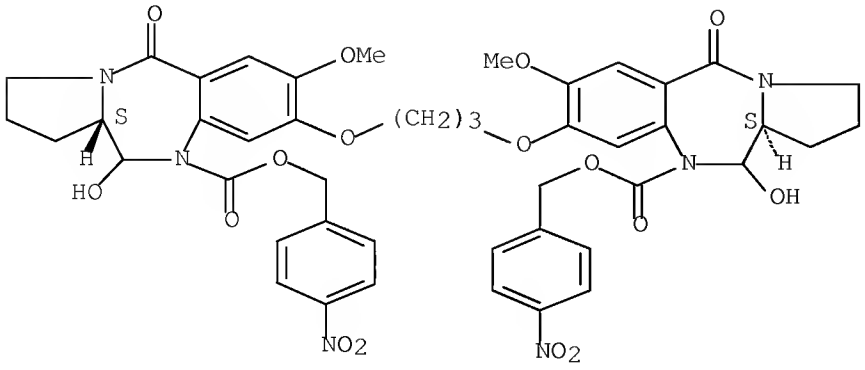
AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein R = (un)substituted (ar)alkyl, etc.; R2 and R3 = independently H, R, OH, OR, =O, =CH-R, =CH2, CH2-CO2R, CH2-CO2H, CH2-SO2R, O-SO2-R, CO2R, COR, or CN; R6, R7, R8, and R9 = independently H, R, OH, OR, halo, NH2, NO2, or Me3Sn; or R7 and R8 together form a -O-(CH2)p-O- group, where p = 1 or 2; or the compound is a dimer with each monomer being the same or different and being of formula I and the R8 groups of the monomers form a -T-R'-T- bridge, where R' is an alkylene chain which may contain ≥ 1 heteroatoms and/or aromatic rings and/or carbon-carbon double or triple bonds, and each T = independently O, S, or N; R10 = a therapeutically removable N-protecting group; R11 = H or R; X is S, O, or NH] were prepared for the treatment of cancer and other site-specific diseases where a local increase of toxicity is beneficial to the patient. Examples include the syntheses of benzyl DC-81, benzyl tomaymycin, and DSB-120 prodrugs starting from 2-nitrobenzoic acid derivs. and pyrrolidines. Data from enzyme and light activation studies and cytotoxicity assays are also given. For example, the nitroreductase-activated benzyl DC-81 (II) was formed in a 6-step sequence involving: (1) benzylation of vanillic acid (67%); (2) ring nitration (82%); (3) amidation with (2S)-pyrrolidinemethanol (88%); (4) reduction of the nitro group (81%); (5) N-addition of 4-nitrobenzyl chloroformate; and (6) cyclization using Swern oxidation conditions (31%). In the presence of nitroreductase and the NADH co-factor, II demonstrated antitumor activity (IC50 = 1-5 μM) against the SW1116 and LS174T human adenocarcinoma colonic cell lines. II proved non-toxic in SW1116 cells at concns. ≤ 500 μM and showed slight toxicity in LS174T cells at concns. > 100 μM. I may also be suitable for treating bacterial, parasitic, or viral infections by exploiting a unique enzyme produced at the site of infection which is not natural to the host, or by exploiting an elevation in the amount of an enzyme which does occur naturally in the host.

IT 260391-43-3P 260391-44-4P 260391-45-5P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compound; preparation of pyrrolobenzodiazepinone prodrugs from 2-nitrobenzoic acid derivs. and pyrrolidines for the treatment of cancer)

RN 260391-43-3 CAPLUS

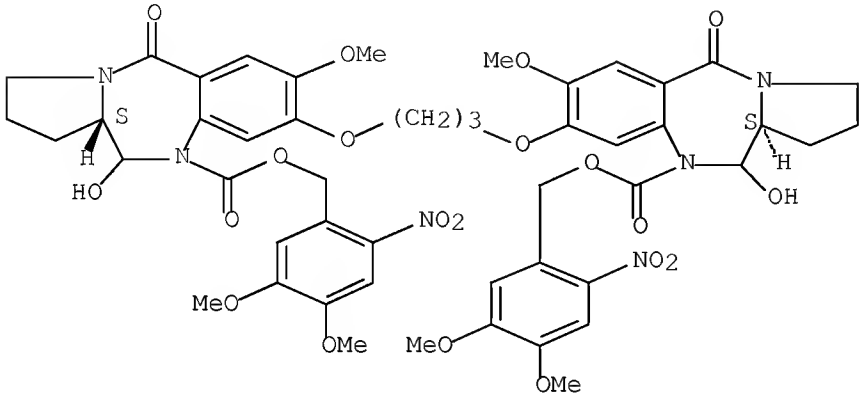
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4-nitrophenyl)methyl] ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



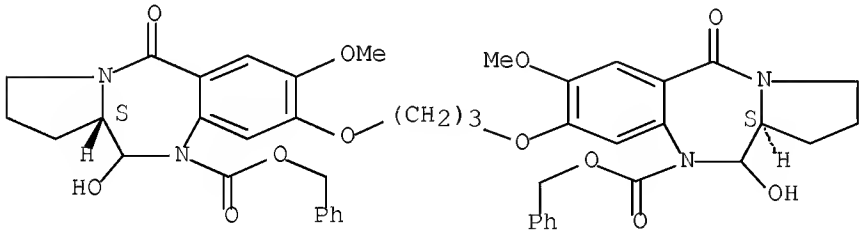
RN 260391-44-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4,5-dimethoxy-2-nitrophenyl)methyl] ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

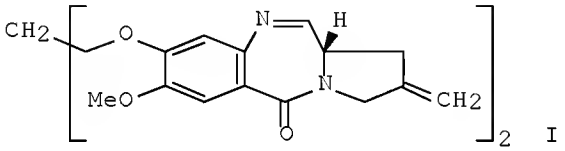


RN 260391-45-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis(phenylmethyl) ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 27 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1999:273645 CAPLUS Full-text
DN 131:116218
TI Synthesis of a novel C2/C2'-exo unsaturated pyrrolobenzodiazepine cross-linking agent with remarkable DNA binding affinity and cytotoxicity
AU Gregson, Stephen J.; Howard, Philip W.; Thurston, David E.; Jenkins, Terence C.; Kelland, Lloyd R.
CS School of Pharmacy and Biomedical Sciences, CRC Gene Targeted Drug Design Research Group, University of Portsmouth, Portsmouth, Hants, PO1 2DT, UK
SO Chemical Communications (Cambridge) (1999), (9), 797-798
CODEN: CHCOFS; ISSN: 1359-7345
PB Royal Society of Chemistry
DT Journal
LA English
GI



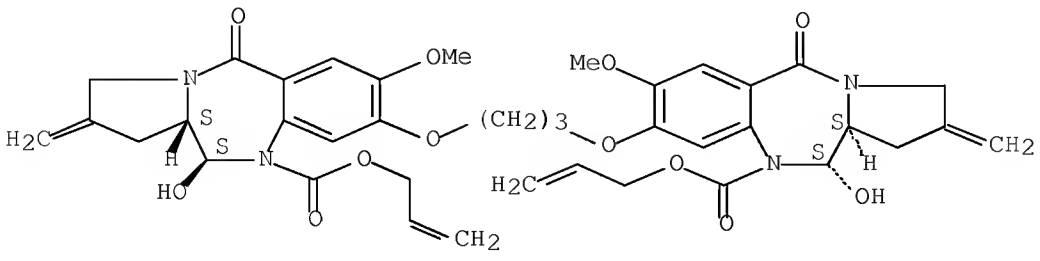
I

AB A C2/C2'-exo unsatd. pyrrolobenzodiazepine dimer (I) has been synthesized which is cytotoxic at the picomolar level and has remarkable covalent DNA binding affinity, raising the melting temperature of duplex-form calf thymus DNA by 34 after 18 h incubation.

IT 232931-64-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation DNA binding and cytotoxicity of pyrrolobenzodiazepine crosslinking agents towards ovarian cancer cells)

RN 232931-64-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-2-methylene-5-oxo-, di-2-propenyl ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



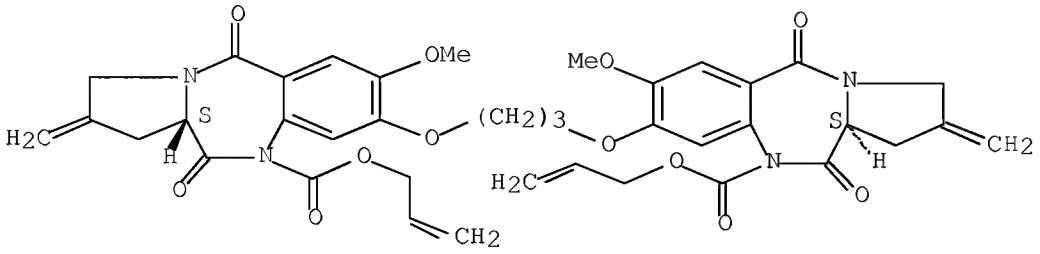
IT 232931-66-7P 232931-67-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation DNA binding and cytotoxicity of pyrrolobenzodiazepine

crosslinking agents towards ovarian cancer cells)

RN 232931-66-7 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-7-methoxy-2-methylene-5,11-dioxo-, di-2-propenyl ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

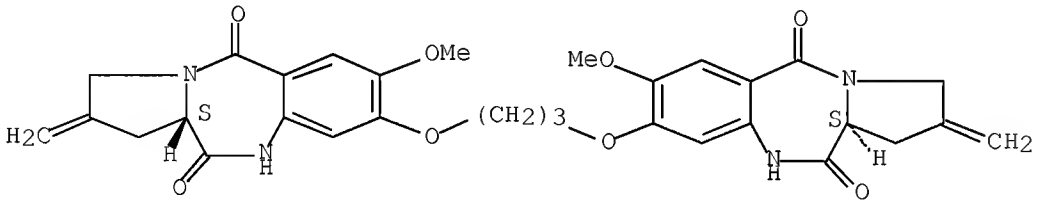
Absolute stereochemistry.



RN 232931-67-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

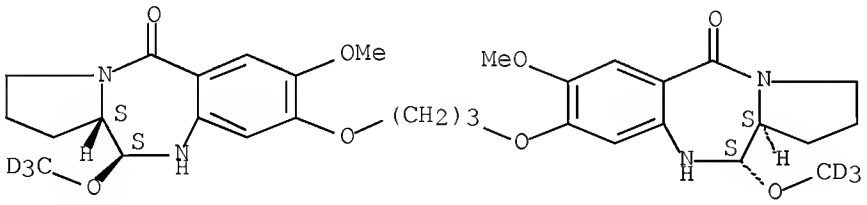
Absolute stereochemistry. Rotation (+).



RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

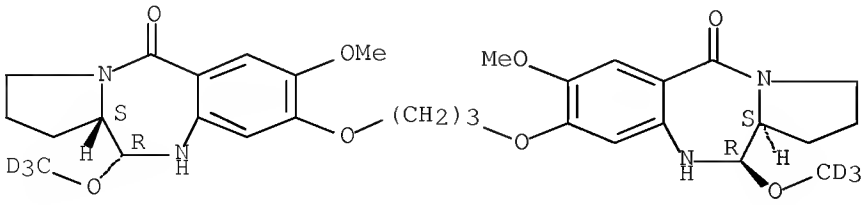
L5 ANSWER 28 OF 28 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1996:644058 CAPLUS Full-text
DN 126:8088
TI Synthesis of Sequence-Selective C8-Linked Pyrrolo[2,1-c][1,4]benzodiazepine Interstrand DNA Crosslinking Agents
AU Thurston, David E.; Bose, D. Subhas; Thompson, Andrew S.; Howard, Philip W.; Leoni, Alberto; Croker, Stephen J.; Jenkins, Terrence C.; Neidle, Steven; Hartley, John A.; Hurley, Laurence H.
CS School of Pharmacy and Biomedical Science, University of Portsmouth, Portsmouth/Hants, PO1 2DT, UK
SO Journal of Organic Chemistry (1996), 61(23), 8141-8147
CODEN: JOCEAH; ISSN: 0022-3263
PB American Chemical Society
DT Journal
LA English
OS CASREACT 126:8088
AB An efficient convergent synthesis of a homologous series of C8-linked pyrrolobenzodiazepine dimers with remarkable DNA interstrand crosslinking activity and potent in vitro cytotoxicity is reported. The "amino thioacetal" cyclization procedure was used to produce the electrophilic DNA-interactive N10-C11 imine moiety during the final synthetic step. In order to construct the key A-ring fragments, a versatile convergent approach has been developed to join two units of vanillic acid with α,ω-dihaloalkanes of varying length to provide the required bis(4-carboxy-2-methoxyphenoxy)alkanes while avoiding the formation of mixts. of monoalkylated and bisalkylated products.
IT 183487-36-7P 183626-03-1P
RL: SPN (Synthetic preparation); PREP (Preparation)(preparation of)
RN 183487-36-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-11-(methoxy-d3)-, [11S-[8(11'R*,11'aR*),11α,11aα]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



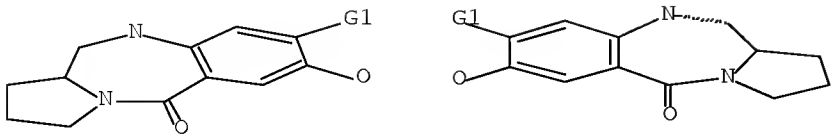
RN 183626-03-1 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,10,11,11a-hexahydro-7-methoxy-11-(methoxy-d3)-, [11R-[8(11'R*,11'aS*),11α,11aβ]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l2; d his; log y
L2 HAS NO ANSWERS
L1 STR



G1 O,S,N

Structure attributes must be viewed using STN Express query preparation.
L2 QUE ABB=ON PLU=ON L1

(FILE 'REGISTRY' ENTERED AT 11:09:53 ON 12 FEB 2008)
DEL HIS Y
L1 STRUCTURE UPLOADED
L2 QUE L1
L3 9 S L2
L4 119 S L2 FUL

FILE 'CAPLUS' ENTERED AT 11:11:23 ON 12 FEB 2008
L5 28 S L4

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	153.56	333.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-22.40	-22.40

STN INTERNATIONAL LOGOFF AT 11:12:33 ON 12 FEB 2008